HCV ASSOCIATED NEPHROPATHY

By

Alaa Sabry, MD, FACP

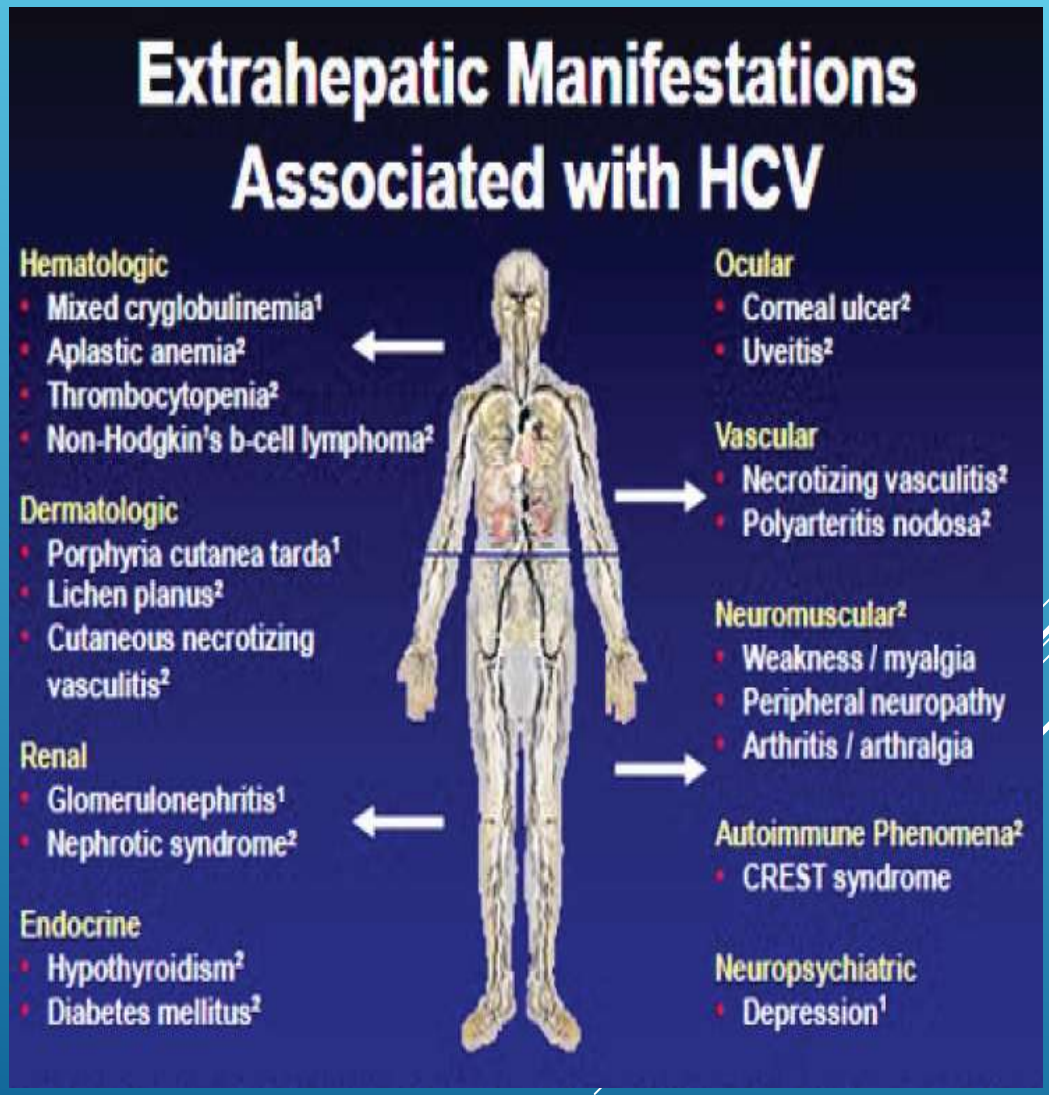
Professor of Nephrology, Mansoura Urology and Nephrology Center

Mansoura University

EXTRAHEPATIC MANIFESTATIONS

- In 1989, the detection of the hepatitis C virus became possible because anti-core antibody was exploited .

- HCV infection is responsible for chronic liver disease and a wide variety of extrahepatic manifestations



- A manifest association between MPGN and a hepatitis C virus (HCV) infection was reported in 1993 -8 patients with MPGN and hepatitis C virus (HCV) infection .

Johnson RJ, et al.. Curr Opin Nephrol Hypertens, 1994

- HCV infection has been reported in association with distinct histological patterns of glomerulonephritis in native kidneys.

1- Membranoproliferative glomerulonephritis:

Tarantino A,Kidney Int 1995.

2-Membranous glomerulonephritis.

3- Focal segmental glomerular sclerosis.

4- Proliferative glomerulonephritis

5- Renal thrombotic microangiopathy associated with anticardiolipin antibodies

6- IgA nephropathy.

7- Diabetic Nephropathy.

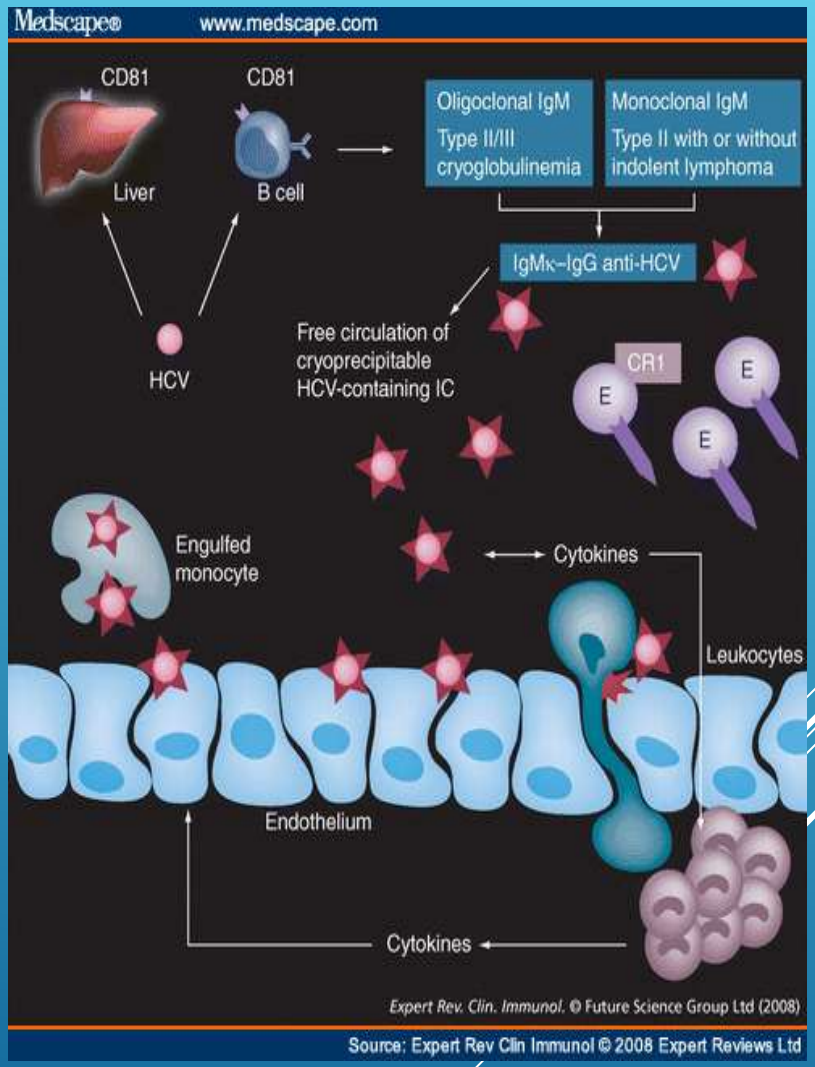
8-Fibrillary and immunotactoid glomerulopathies.

PATHOGNESIS

CRYOGLOBULINEMIC MPGN

- The prevalent pathogenetic mechanism in HCV-associated GN is the deposition in the glomerulus of a monoclonal IgM rheumatoid factor with particular affinity for the glomerular matrix .
- The IgM RF can deposit alone or as a mixed IgG-IgM cryoglobulin, not necessarily bound to HCV-derived antigens .
- It is possible that in a minority of cases immune complexes composed of HCV antigens and anti-HCV IgG antibodies can deposit directly in the glomerular structures in the absence of a concomitant type II mixed cryoglobulin with a monoclonal IgM R.
- An MPGN very similar to human cryoglobulinaemic was induced in mice by intravenous injection of solubilized type II mixed cryoglobulins from patients with this renal disease and HCV infection

(Fornasieri A *et al. Lab Invest* 1993) .



THE JOURNAL OF IMMUNOLOGY

Role of the Receptor for the Globular Domain of C1q Protein in the Pathogenesis of Hepatitis C Virus-Related Cryoglobulin Vascular Damage

Domenico Sansonno, Felicia Anna Tucci, Berhane Ghebrehiwet, Gianfranco Lauletta, Ellinor I. B. Peerschke, Vincenza Conteduca, Sabino Russi, Pietro Gatti, Loredana Sansonno and Franco Dammacco

J Immunol 2009; 183:6013-6020; Prepublished online 14 October 2009;

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- gC1q-R is a 33 kDa acidic protein expressed on somatic cells . It binds to the globular heads of C1q and modulates complement activation.
- Efficient engagement of C1q protein by cryoglobulins may be an important pathogenetic mechanism involved in the cryoglobulin-related pathway.
- Engagement of circulating HCV core protein with gC1q-R on the surface of B lymphocytes provides the virus with a direct means of affecting host immunity.
- HCVcore-gC1q-R interaction has been assumed to play a critical role in modulating the T cell immune response.
- gC1q-R exacerbates inflammation by generating vasoactive peptides from the complement system and bradykinin from the contact system .

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Patients and controls

Thirty-two patients with MC positive for anti-HCV Abs and circulating HCV RNA .
Liver biopsies showed features of chronic active hepatitis (CAH).

Twenty additional patients had a diagnosis of CAH and chronic HCV infection without MC.

A significant increase of soluble gC1q-R levels was demonstrated in MC patients compared with the HCV-infected patients without MC and the healthy controls.

A positive correlation between circulating gC1q-R and plasma levels of RF activity and C1q concentration in MC patients was shown.

After pegylated IFN- and RBV combination therapy:

Improvements of general signs and cutaneous vasculitis were associated with decrement of circulating levels of soluble gC1q-R.

No changes from the basal values were noted in the nonresponders

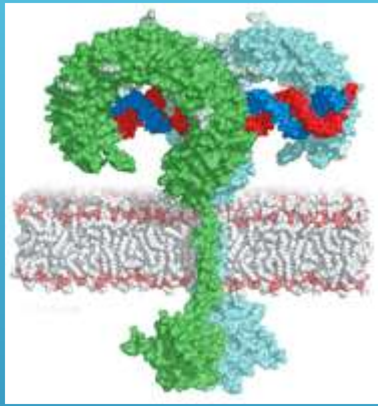
American Journal of Pathology, Vol. 168, No. 2, February 2006

Cardiovascular, Pulmonary and Renal Pathology

Novel Role of Toll-Like Receptor 3 in Hepatitis C-Associated Glomerulonephritis

Markus Wörnle,* Holger Schmid,* Bernhard Banas,† Monika Merkle,* Anna Henger,* Maximilian Roeder,* Simone Blattner,* Elisabeth Bock,* Matthias Kretzler,* Hermann-Josef Gröne,† and Detlef Schlöndorff*

- TLRs expressed on immune cells but also on a number of nonimmune cells.
- Eleven members of the TLR family (TLR1 to TLR11) in humans, each recognizing a distinct component of infectious agents .



- We postulate that TLR3 may be important for the clearance of viral RNA reaching the glomerular mesangium, possibly serving in a housekeeping manner under normal conditions.
- Under conditions of viral infection with immune stimulation, enhanced levels of IFN-, TNF-, and IL-1 would upregulatee TLR3 on MCs, and the increased amounts of viral RNA reaching MCs would result in the generation of chemokines.
- The chemokines would initially attract neutrophils (IL-8/CXCL8), followed by macrophages (RANTES/CCL5, MCP-1/CCL2).
- During pathological conditions such as viral infections, viral RNA alone or as part of immune complexes could reach the mesangium and trigger glomerular inflammation, resulting, eg, in HCV-associated glomerulonephritis.

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DOI: 10.2353/ajpath.2006.050491

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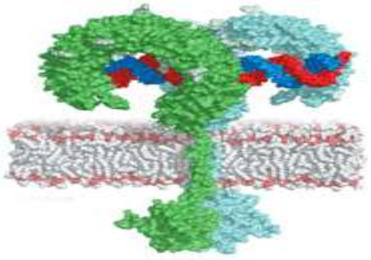
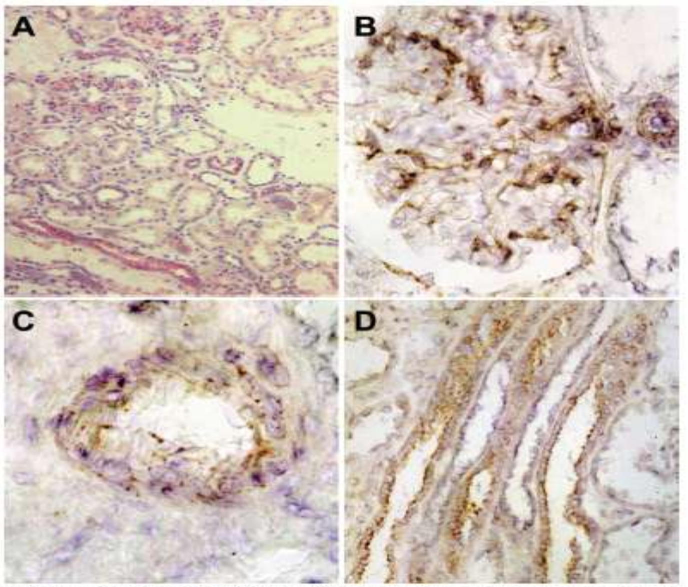




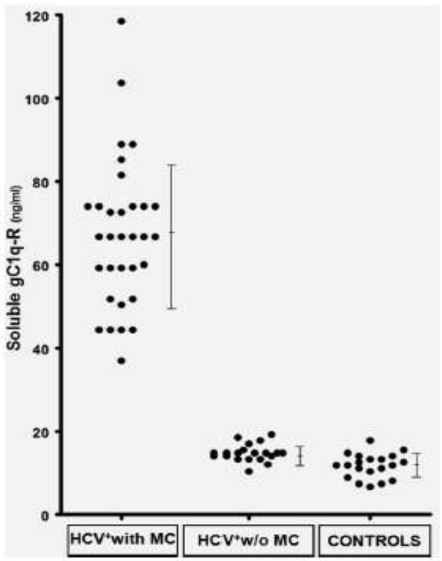


FIGURE 1. Serum levels of soluble gC1q-R in sera of different categories of patients and in the healthy subjects.

Scandinavian Journal of Clinical & Laboratory Investigation, 2011; 71: 456–461

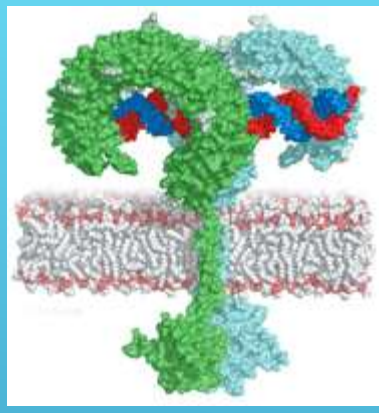
informa
healthcare

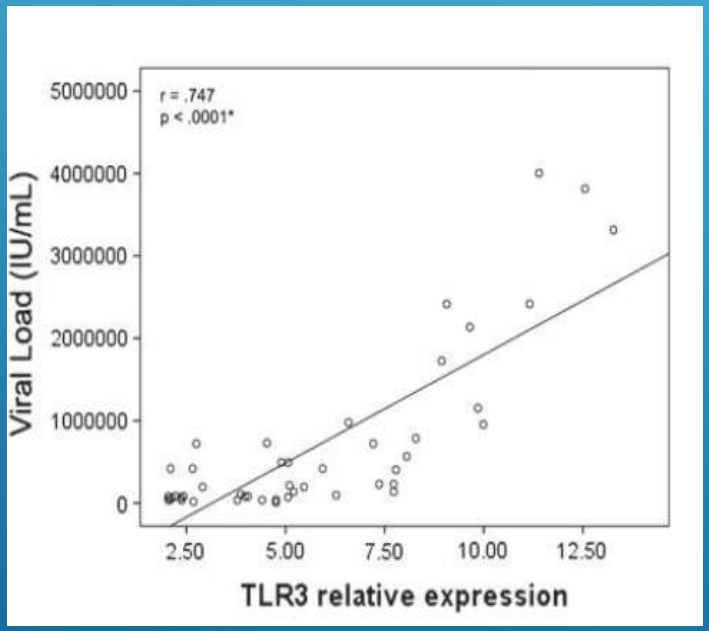
ORIGINAL ARTICLE

Toll-like receptor 3 gene expression in Egyptian patients with glomerulonephritis and hepatitis C virus infection

ABLA A. ABOU-ZEID[1] & HESHAM K. EL-SAYEGH[2]

Departments of [1]Clinical Pathology, [2]Internal Medicine, Faculty of Medicine, Alexandria University, Alexandria, Egypt





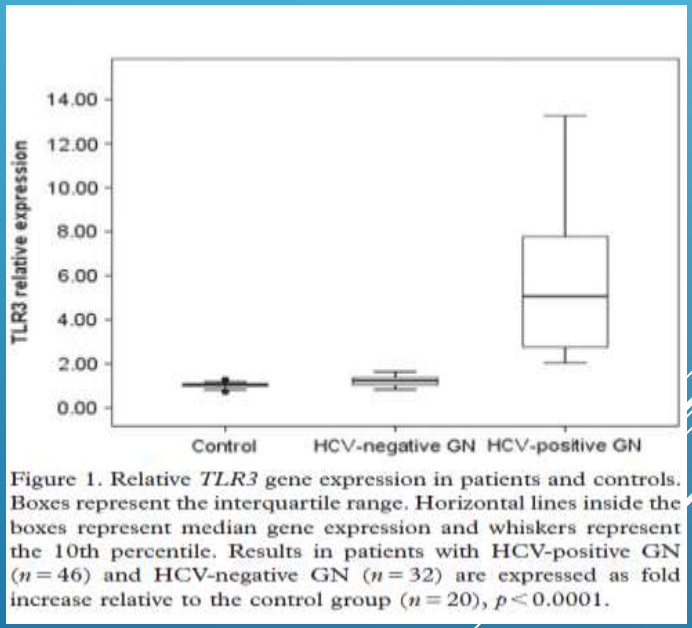
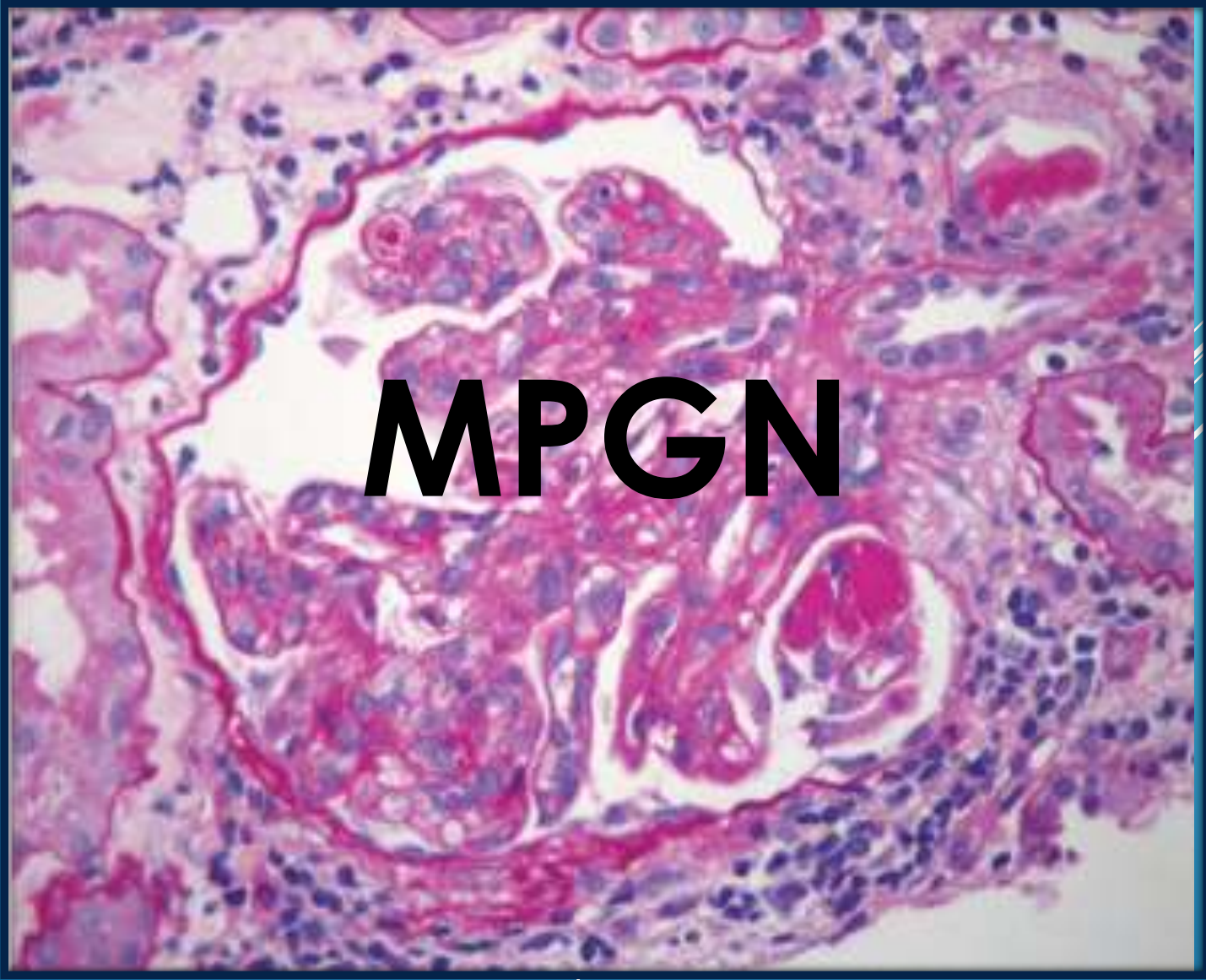


Figure 1. Relative *TLR3* gene expression in patients and controls. Boxes represent the interquartile range. Horizontal lines inside the boxes represent median gene expression and whiskers represent the 10th percentile. Results in patients with HCV-positive GN ($n = 46$) and HCV-negative GN ($n = 32$) are expressed as fold increase relative to the control group ($n = 20$), $p < 0.0001$.

PATHOLOGY

MPGN



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Virology 334 (2005) 10–16
VIROLOGY
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HCV associated glomerulopathy in Egyptian patients: Clinicopathological analysis

Alaa Sabry[a,*], Amgd E-Agroudy[a], Hussein Sheashaa[a], Amr El-husseini[a], Nohir Mohamed Taha[b], Mahmoud Elbaz[b], Mohamed Sobh[a]

Table 1
Results of renal biopsy in 233 Egyptian patients with glomerulopathy

Histological classes	Frequency	Percent
Membranoproliferative GN	91	39
Focal segmental glomerulosclerosis	71	30.4
Diffuse Mesangioproliferative GN	30	12.8
Membranous nephropathy	10	4.29
Focal mesangial proliferative GN	8	3.4
Crescentic glomerulonephritis	5	2.14
Minimal change Nephropathy	4	1.71
Amyloidosis	4	1.71
IgA nephropathy	3	1.71
Normal by light microscopy	3	1.2
Tubulo interstitial fibrosis	2	0.8
Diabetic glomerulosclerosis	1	0.4
End stage renal disease	1	0.4
Total	233	100

* GN = glomerulonephritis.

Table 4
Histological diagnosis of HCV-positive patients

Histological diagnosis	(*n* = 50)
Membranoproliferative glomerulonephritis type 1	27
Monocyte infiltration	17
Intraluminal hyaline thrombi	6
Accentuated lobular architecture	5
Focal segmental glomerulosclerosis	12
Membranous nephropathy	2
Mesangioproliferative glomerulonephritis	9

Histological evaluation of renal biopsies from the 233 patients revealed MPGN and focal segmental glomerulosclerosis as the most common lesions observed accounting for 39% and 30.4%, respectively, among 233 patients presented with glomerulopathy

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Table 3
Demographic and clinical characteristics for cryoglobulinemic and non-cryoglobulinemic patients (median and confidence interval)

Parameters	Cryoglobulinemic (n = 27)	Non-Cryoglobulinemic (n = 23)	P value
Age	40 (35.97–43.95)	45 (38.69–46.60)	0.283
Gender	Male, 17	18	0.239
Anasarca	16	14	0.908
Jaundice	3	3	0.834
Hypertension	15	13	0.945
Past history for blood transfusion	13	7	0.203
Serum creatinine	1.43 ± .49	1.21±	0.16
Serum complement C3	90.40 ± 46.18	116.24 ± 51.88	0.07
Serum complement C4	30.95 ± 11.6	33.1 ± 11.95	0.89

Among the 50 HCV-positive patients 27 were cryoglobulinemic, 18 patients were positive for rheumatoid factor, mean serum creatinine was 1.2 mg/dl, 24 h protein excretion was 3.7 g, and their levels of C 3 were normal but low for C4

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The high prevalence of MPGN in areas endemic for HCV could be attributed to such infection.
MPGN-associated with HCV has peculiar histological features.

CLINICALLY

1- Proteinuria and microscopic hematuria.

2-Nephrotic syndrome .

3-Acute nephritic syndrome, with rapid deterioration of renal function, are observed in, respectively, 20 and 25% of patients.

4-Fifty percent of patients have moderate renal insufficiency, and hypertension is present in 80% of patients.

5-Extra-renal manifestations. The most frequently observed are purpura, arthralgia and peripheral neuropathy.

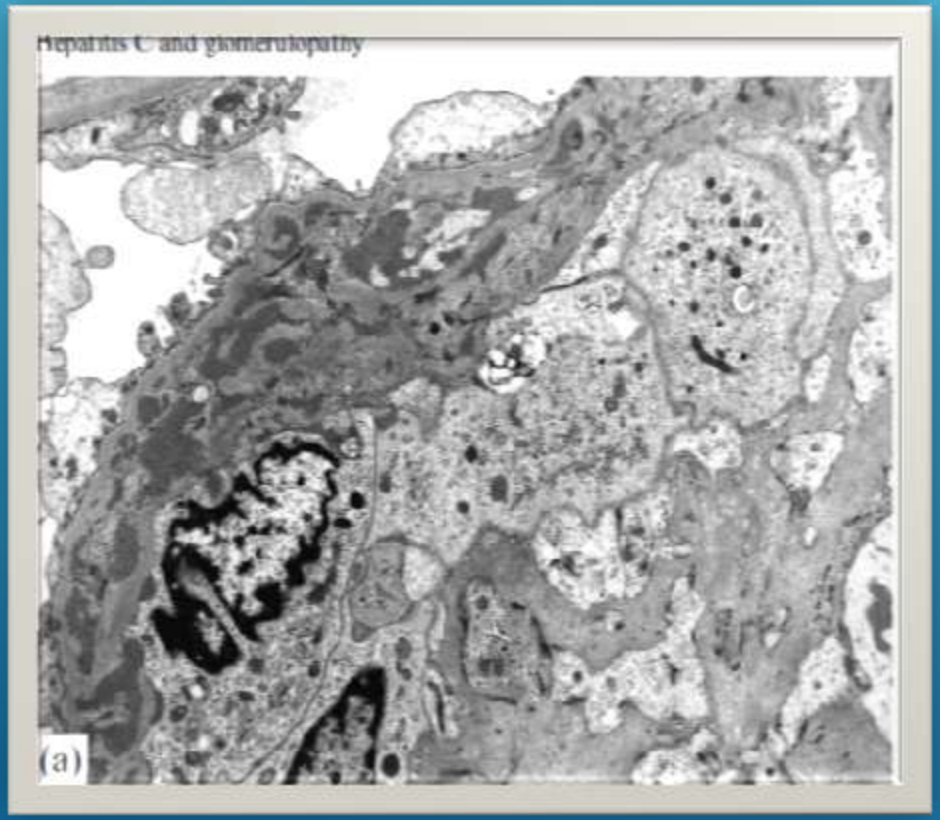
Nephrol Dial Transplant (2002) 17: 239–245

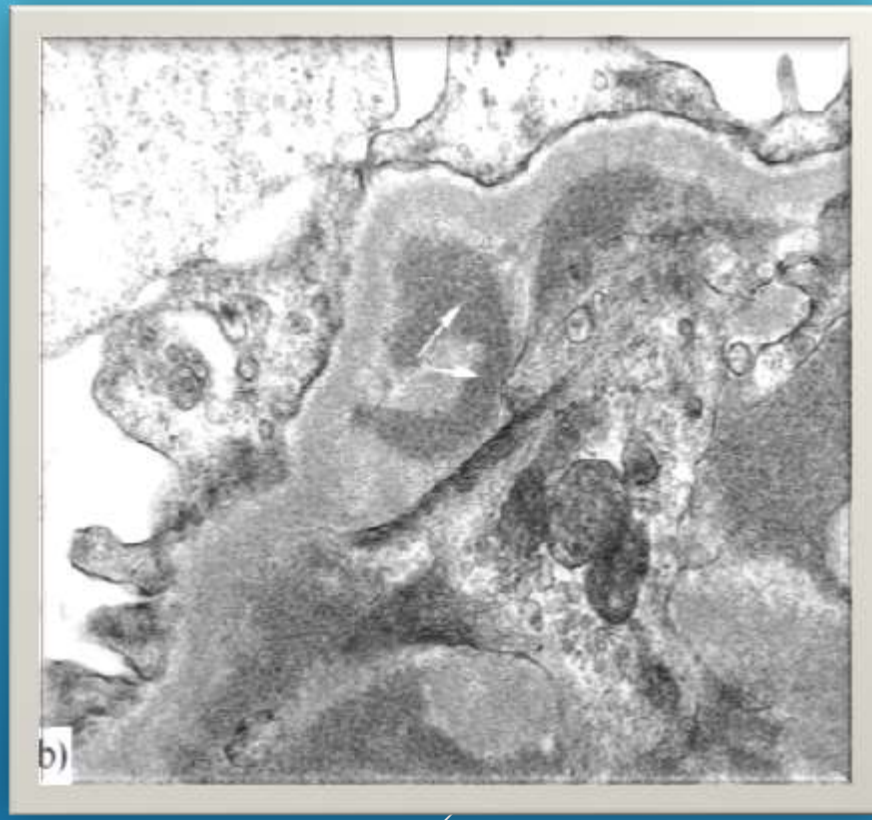
Nephrology
Dialysis
Transplantation

Original Article

A comprehensive study of the association between hepatitis C virus and glomerulopathy

Alaa A. Sabry[1,2], Mohamed A. Sobh[2], William L. Irving[3], Anna Grabowska[3], Bart E. Wagner[4], Samantha Fox[5], Gura Kudesia[5] and A. Meguid El Nahas[1]





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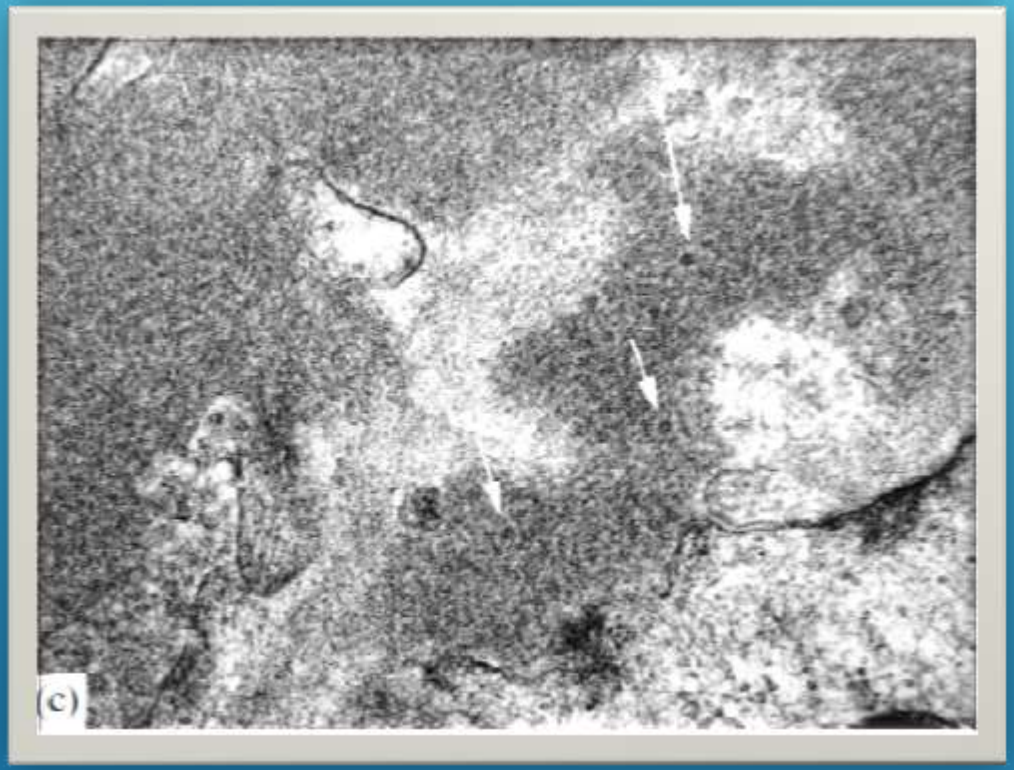

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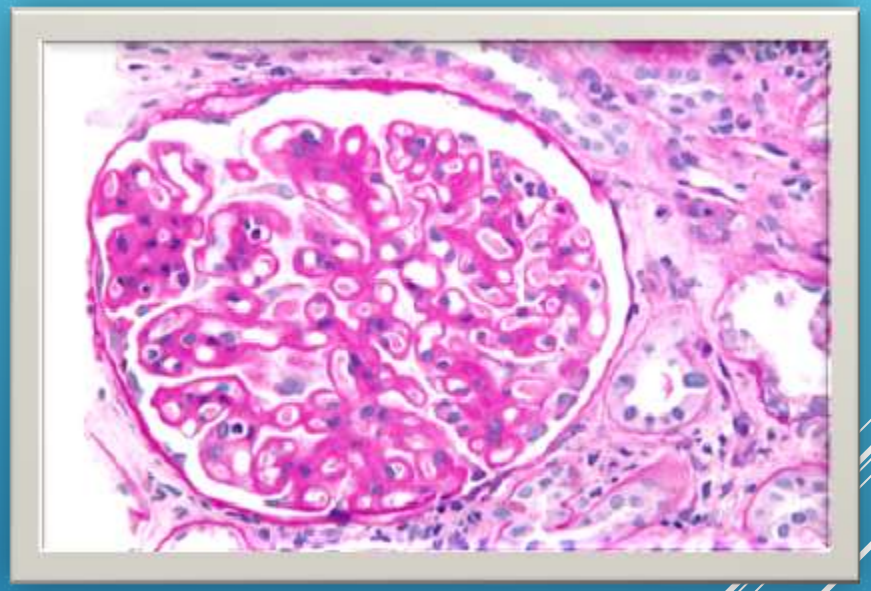
In conclusion, the prevalence of HCV infection is higher among Egyptian patients with chronic glomerulonephritis when compared to the general population.
Our recommendation is to screen all patients with MPGN in endemic areas for HCV infection.
Finally, combination of EM and PCR could help to establish diagnosis.

2.MEMBRANOUS GLOMERULONEPHRITIS

- The clinical presentation and the biopsy features of MGN in patients with HCV infection are similar to those of idiopathic MGN .



- Normal complement levels
- The absence of cryoglobulins and rheumatoid factors in the serum.

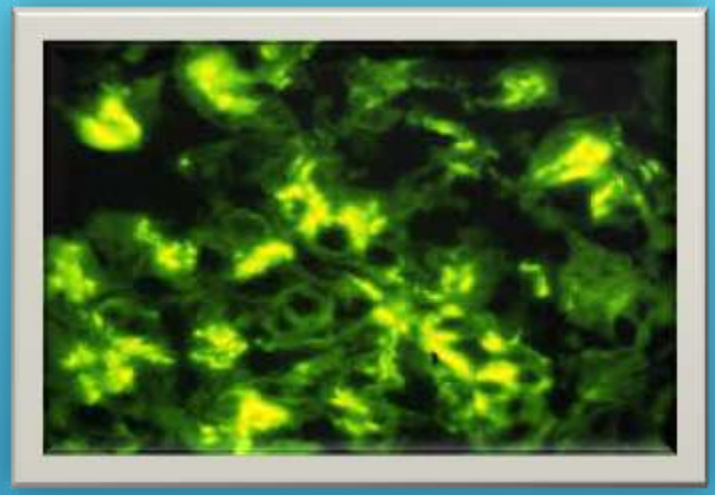
- A Japanese group detected HCV core protein in the glomeruli of two patients with MGN, suggesting that immune complexes containing HCV proteins might be deposited in the glomeruli .

  (Okada K, et al. Clin Nephrol 1996).

- It is probably advisable to seek serologic evidence of HCV infection in all cases of biopsy-proven membranous nephropathy

3-IGA NEPHROPATHY

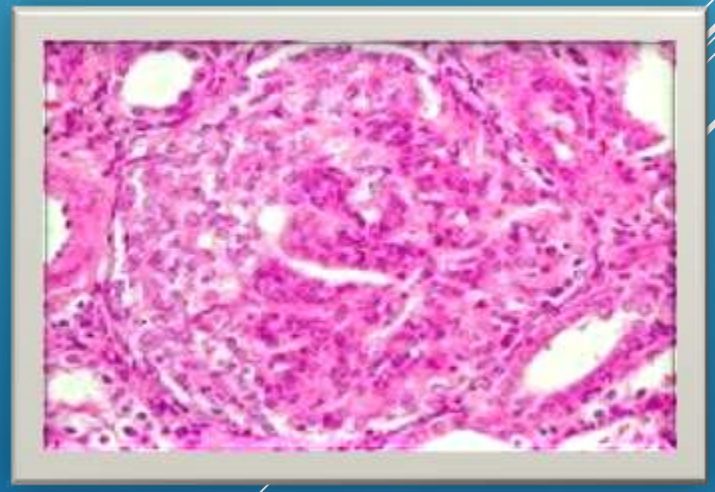
- A handful of studies have documented the development of IgA nephropathy (IgAN) in patients with HCV infection.
- The biopsy features of IgAN associated with HCV infection are similar to those encountered in other forms of IgAN.
- Circulating immune complexes containing IgA and HCV antigens have not been reported.



4-RPGN

- Development of rapidly progressive, pauci-immune, crescentic GN has been described in one patient with HCV infection.

(Usalan C, Clin Nephrol 1998)



- Serologic studies, including tests for cryoglobulins and anti-neutrophil cytoplasmic, anti-glomerular basement membrane, and anti-nuclear antibodies, were all negative.
- The relationship between the glomerular disease and viral hepatitis in this patient is unclear.

4-Diabetic nephropathy

- Several studies have documented an association between HCV infection and non-insulin-dependent diabetes mellitus.

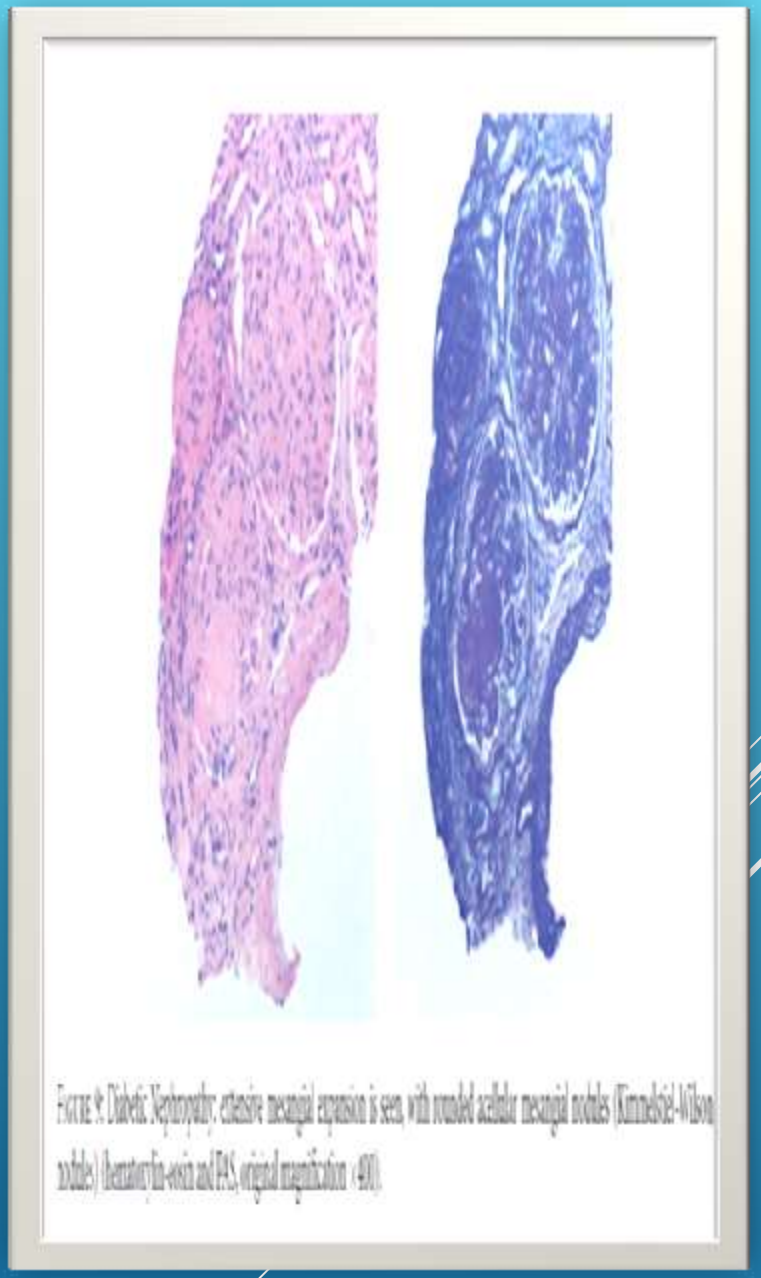
  (el-Zayadi AR, et al.*World J Gastroenterol* 2012)

- A high prevalence of HCV infection was found in patients with diabetic nephropathy.

- The slope of reciprocal serum creatinine was significantly greater in the HCV-positive than in HCV-negative patients with type II diabetic-related glomerulosclerosis.

- HCV was also found to be a predictor factor of poorer renal survival in diabetic patients .

  (Sara E. Miller. Saudi J Kidney Dis Transplant 2000)



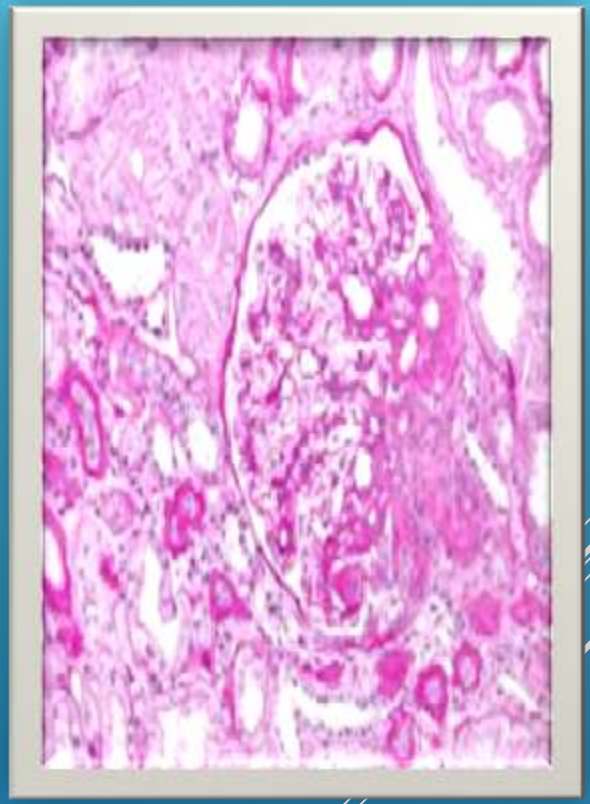
5- FSGS

- Association between HCV and FSGS was first noted by Altraif et al. in 1995 when patients with HCV cirrhosis underwent kidney biopsy for proteinuria.

(Altraif, I.H. Am. J. Nephrol., 15 (1995), 407–410).

- FSGS has also been attributed anecdotally
- to IFN-a therapy for HCV infection.

- In some cases, it has been unclear whether the renal dysfunction was a result of the therapy, the underlying disease process, or a combination of the two.

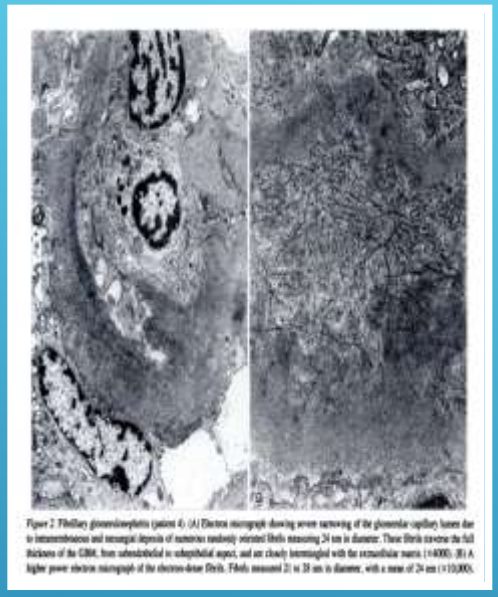


J Am Soc Nephrol 9: 2244–2252, 1998

Hepatitis C Viral Infection Is Associated with Fibrillary Glomerulonephritis and Immunotactoid Glomerulopathy

GLEN S. MARKOWITZ,* JEN-TSE CHENG,† ROBERT B. COLVIN,‡ WAYNE M. TREBBIN,§ and VIVETTE D. D'AGATI*

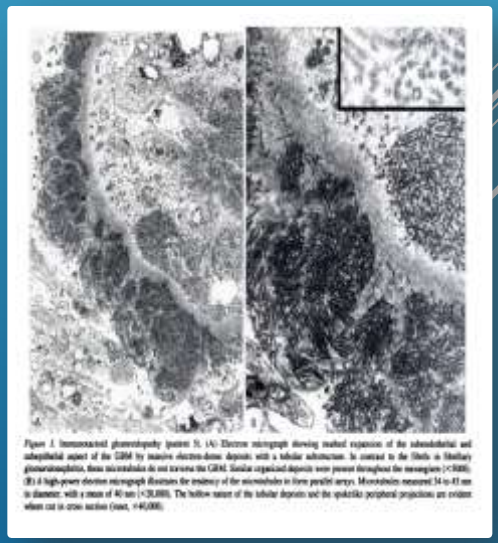
- Many cases of fibrillary glomerubonephritis and immunotactoid glomerulopathy (ITO) associated with hepatitis C virus infection.



- Hematuria,
- Proteinunia,
- Hypertension,
- Renal insufficiency
- A poor prognosis with mean course to renal failure of less than 2 yr .

- Light microscopy reveals mesangial and frequently endocapillary hypercellularity, often with crescents

(Iskandar , et al .*Kidney mnt* 42: 1401-1407, 1992)



- However, the single previous report of HCV infection associated with FGN demonstrated improvement in renal function, urinary protein excretion, and urine sediment abnormalities after administration of 9 million units of alpha interferon weekly for 3 mo .

(Coroneos E, *Am J Kidney Dis* 29:et al 132-135, 1997).

RENAL MANIFESTATIONS ASSOCIATED WITH THERAPEUTIC AGENTS

1- Acute Kidney Injury

Quesada JR,. J Clin Oncol 1986.

2-Acute interstitial nephritis.

Allon M, Am J Med 1988.

3-Minimal change glomerulopathy.

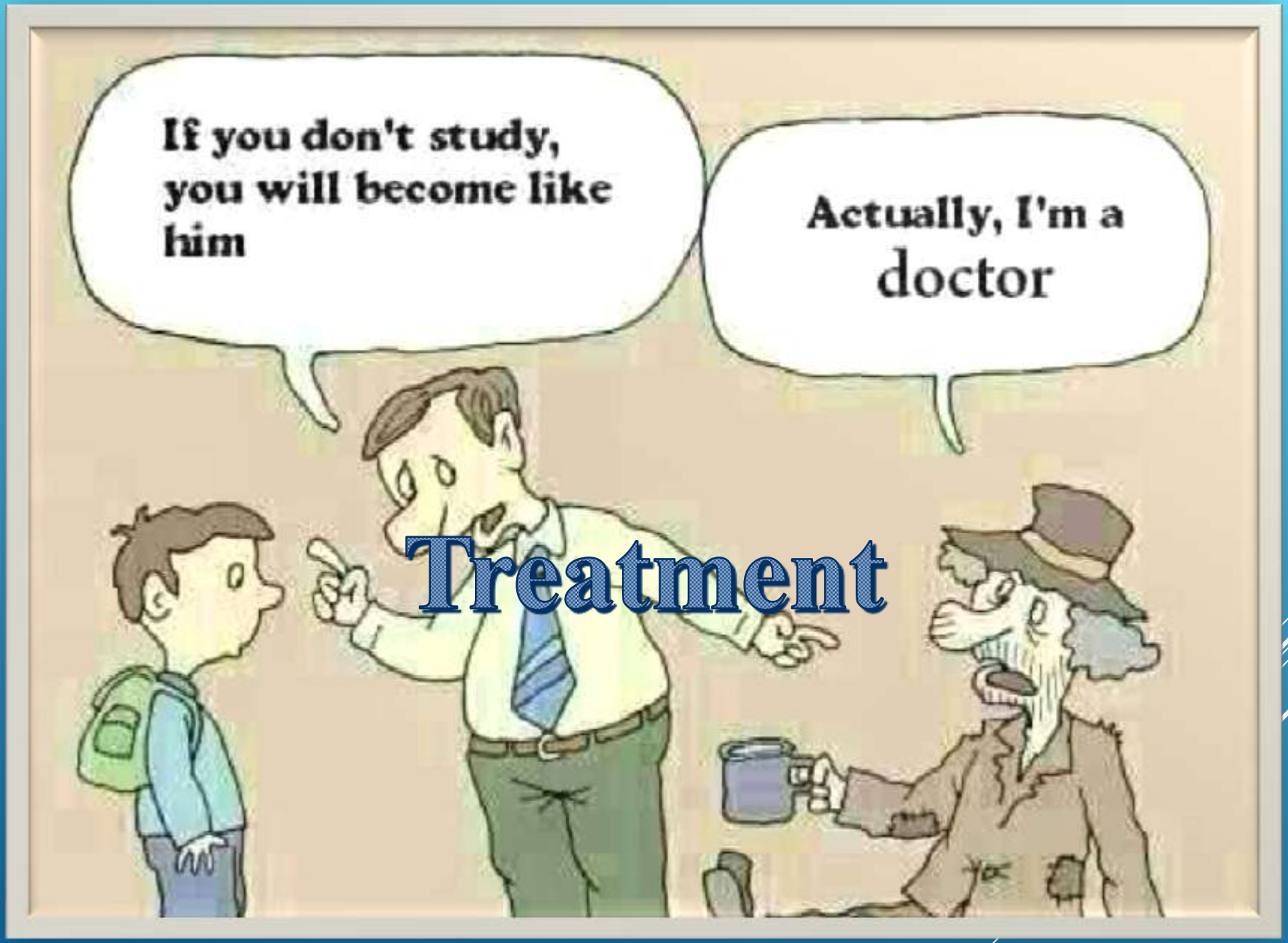
Traynor A,. Nephron 1994.

4- Thrombotic microangiopathy (TMA)

Honda K. Am J Kidney Dis 1997;30:123-30.75

therapy with IFN-a for hematopoietic malignancies

Sara E. Miller Saudi J Kidney Dis Transplant 2000


If you don't study, you will become like him
Actually, I'm a doctor
Treatment

1-Symptomatic therapy

2-Immunosuppressive therapy

3- Antiviral therapy:

IFN monotherapy.

Combination (IFN + Riba).

DAA

4- Rituximab:

Monotheraoy

Triple

5- New approaches

1-IMMUNOSUPPRESSIVE THERAPY

Before the HCV era, a combination of corticosteroids and immunosuppressants, such as cyclophosphamide and azathioprine, had been used for the control of severe cryovas lesions.

1- Steroids:

Alone or in addition to IFN-a, did not favourably affect the response of HCV-cryovas manifestations in two controlled studies.

(Dammacco F, et al. Blood 1994)
(Casato M .. Blood 1997)

In one randomised trial, methylprednisolone given alone for 1 year was associated with a clinical response in 16.7% of patients compared with 53.3% and 52.9% in patients receiving IFN-a or IFN-a plus methylprednisolone, respectively.

Low-dose corticosteroids may help to control minor intermittent inflammatory signs such arthralgia but they do not succeed in cases of major organ involvement eg neurologic, renal, cardiac) or in the long-term control of vasculitis.

Previous uncontrolled studies that included small number of patients treated with these therapies showed that this regime often controlled the acute phase of the disease ,but was often poorly tolerated.

The flare-up of HCV RNA concentration observed during immunosuppressive therapy may be harmful to HCV related-liver disease.

1-IMMUNOSUPPRESSIVE THERAPY

2-Cyclophosphamide :

- Cyclophosphamide was used successfully -suppressing B lymphocyte stimulation and cryoglobulins production- for the treatment of HCV-infected patients with cryoglobulinemia and progressive renal insufficiency caused by MPGN. Unfortunately, HCV-RNA levels also increased .

(Fabrizi F. Semin Nephrol 2002)
(Quigg RJ, Am J Kidney Dis 1995)

3-Plasma exchange :

- In the past, patients with mixed cryoglobulinemia, with or without renal involvement, were treated by plasma exchange to remove circulating cryoglobulins from the plasma and, consequently, to diminish the deposition of immune complexes in the kidney.
- Immunosuppressive therapy is usually needed in addition to plasma exchange in order to avoid the rebound increase in cryoglobulin serum levels seen after discontinuation of apheresis.

(Hausfater P et al.Nephron 2002)

- In a retrospective study of 105 patients with renal disease associated with cryovas, 80% of patients received corticosteroids and/or cytotoxic agents, while 67% underwent plasmapheresis .
- Despite this aggressive approach, long-lasting remission of the renal disease was achieved in only 14% of cases, and the 10-year survival rate was only 49%.

(Tarantino A. Kidney Int 1995).

ANTI-HCV THERAPY

- *Interferon-alpha:* In the early 1990s, standard alpha-interferon (a-IFN) was used alone at different doses, i.e. 3 to 10 MU three times a week: unfortunately, the results were disappointing.

- **14 patients** experiencing an HCV-related glomerulonephritis were treated with a-IFN for 6–12 months. Overall, proteinuria significantly decreased, whereas renal function remained stable. In 11 patients, sera were tested for HCV RNA while on this therapy. Patients who became cleared of HCV RNA (N= 6) had a better outcome compared to those who remained HCV RNA positive (N=5).

(Johnson, RJ , et al. Kidney Int 1994)

- Misiani et al. reported an improvement in renal function In contrast, there was no effect on proteinuria. All patients relapsed after a-IFN therapy was stopped.

(Misiani R et al. N Engl J Med 1994).

- A virologic response at the end of treatment was reported in 15–50% of patients receiving IFN monotherapy; however, most of the responders developed a virologic and clinical relapse following IFN withdrawal .

(Liang TJ, Ghany MG. N Engl J Med 2013).

COMBINED THERAPY PEGYLATED IFN, WITH RIBAVIRIN

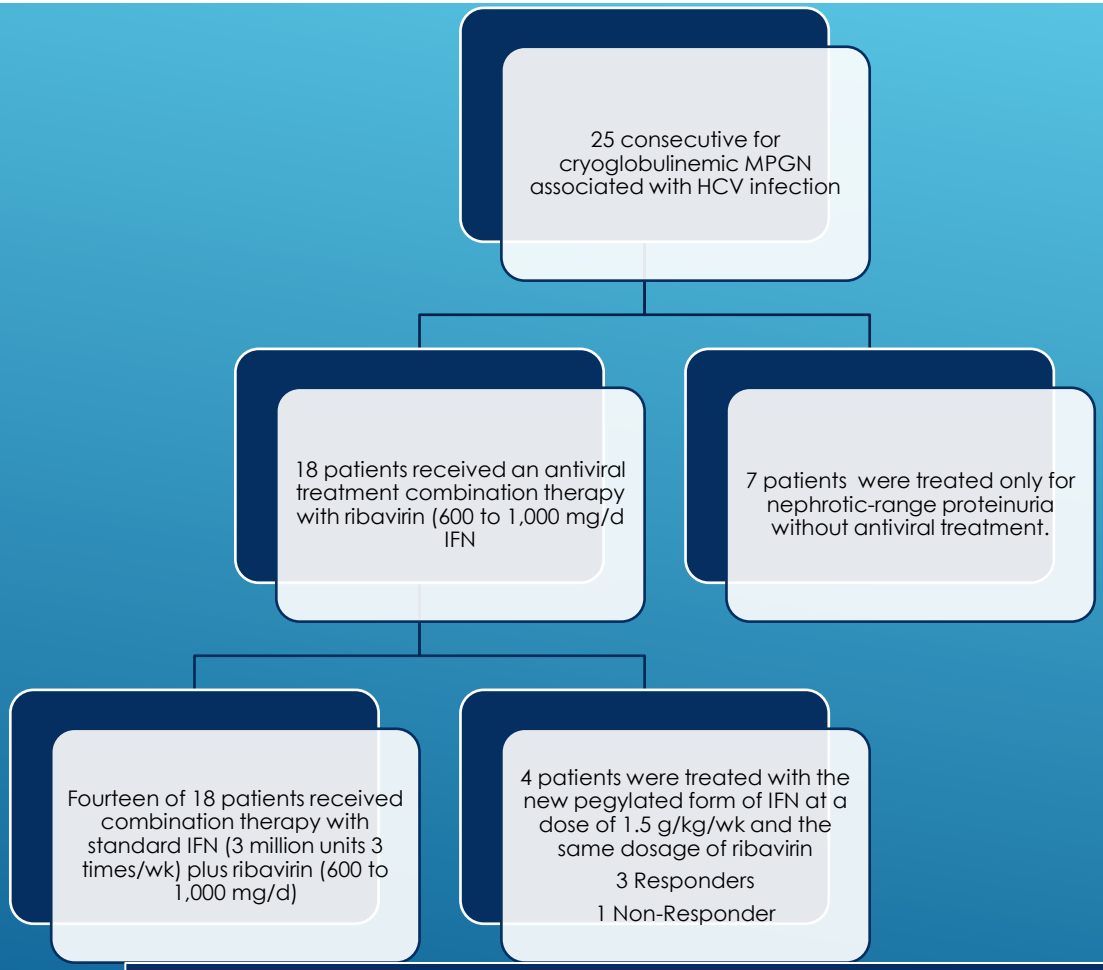
IFN AND RIBAVIRIN

- It has been found to be more effective than a-IFN alone.
- It provides the best chance of viral clearance and subsequent disease improvement.
- the IFN plus ribavirin combination showed increased efficacy on the main HCV-related vasculitic manifestations:

  (cutaneous, 100%; renal,50%; nerve, 25–75%).
- Most patients (75%) with negative viraemia at the end of follow-up were complete clinical responders for cryova.

Influence of Antiviral Therapy in Hepatitis C Virus–Associated Cryoglobulinemic MPGN

Laurent Alric, MD, PhD, Emmanuelle Plaisier, MD, Sophie Thébault, MD, Jean-Marie Péron, MD, PhD, Lionel Rostaing, MD, PhD, Jacques Pourrat, MD, Pierre Ronco, MD, Jean-Charles Piette, MD, and Patrice Cacoub, MD



American Journal of Kidney Diseases
Volume 43, Issue 4 , Pages 617-623, April 2004

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Table 3. Influence of Antiviral Treatment on Renal Disease

	Group 1a; Sustained Virological Responders (n = 12)	Group 1b; Nonresponders (n = 6)	Group 2; Controls (n = 7)
Proteinuria (g/d)			
Initial evaluation	2.85 ± 2.2	3.5 ± 2.1	3.6 ± 1.9
End IFN + ribavirin	1 ± 1.4*	1.1 ± 0.4†	—
End of follow-up	0.4 ± 0.8‡§‖	1.18 ± 0.5	3.3 ± 3.1
Serum creatinine (mg/dL)			
Initial evaluation	1.3 ± 0.5	1.4 ± 0.6	1.5 ± 0.5
End IFN + ribavirin	1.2 ± 0.5	1.2 ± 0.2	—
End of follow-up	1.4 ± 0.6	1.6 ± 0.7	1.3 ± 0.4
Serum albumin (g/dL)			
Initial evaluation	2.98 ± 0.51	3.31 ± 0.45	3.31 ± 0.41
End IFN + ribavirin	3.63 ± 0.69*	3.8 ± 0.21	—
End of follow-up	4 ± 0.56†	3.47 ± 0.45	3.2 ± 0.68
Cryoglobulinemia (g/L)			
Initial evaluation	1.38 ± 2.2	1.5 ± 1	1.08 ± 0.9
End IFN + ribavirin	0.29 ± 0.4*	0.58 ± 0.5	—
End of follow-up	0.25 ± 0.4‡	0.92 ± 0.35	0.78 ± 0.7
Cryoglobulin clearance	5	0	0

NOTE. Values expressed as mean ± SD. To convert serum creatinine in mg/dL to μmol/L, multiply by 88.4; serum albumin in g/dL to g/L multiply by 10.

*$P < 0.05$ before treatment versus end of treatment.

†$P = 0.05$ before versus end of treatment in group 1b.

‡$P < 0.05$ before treatment versus end of follow-up.

§$P < 0.05$ responders versus nonresponders.

‖$P < 0.05$ responders versus controls at the end of follow-up.

American Journal of Kidney Diseases 2004

Nephrol Dial Transplant (2002) 17: 1924–1930

Nephrology
Dialysis
Transplantation

Original Article

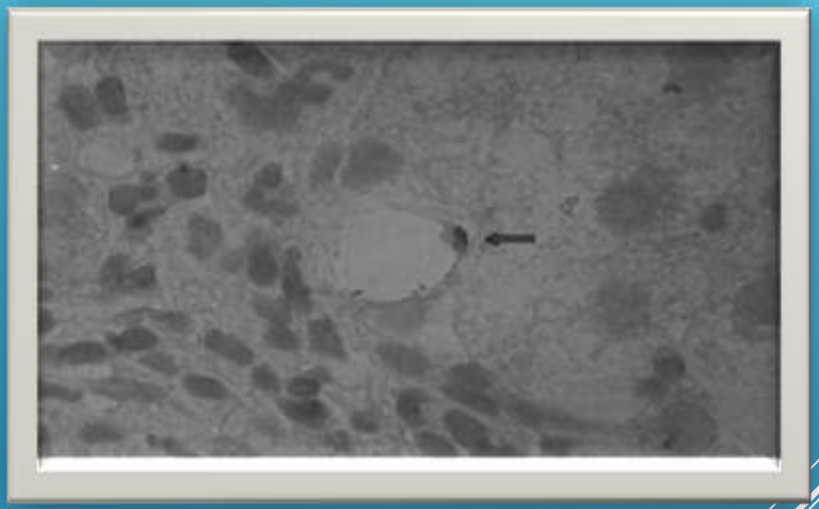
Effect of combination therapy (ribavirin and interferon) in HCV-related glomerulopathy

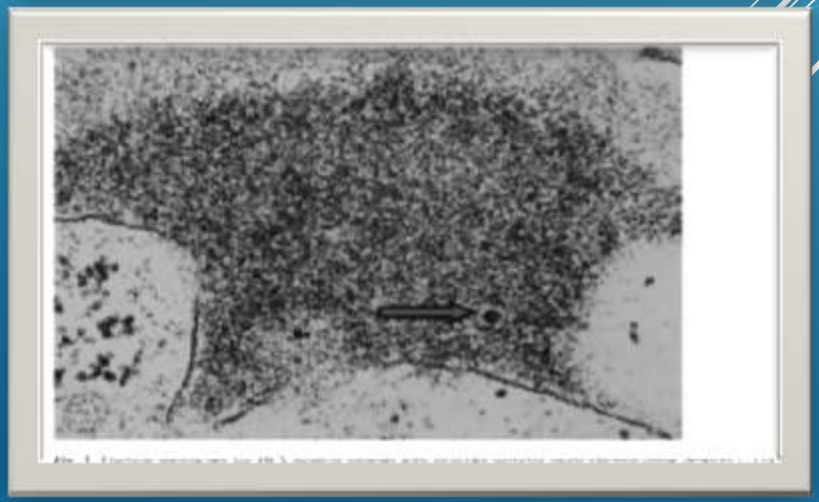
Alaa A. Sabry[1], Mohamed A. Sobh[1], Hussein A. Sheaashaa[1], Guara Kudesia[2], Graham Wild[2], Samantha Fox[2], Bart E. Wagner[2], William L. Irving[3], Anna Grabowska[3] and Abdel Meguid El-Nahas[3]

Table 1. Demographic, clinical, and histological characteristics of 20 patients on interferon-α therapy

Characteristic	Number
Demographic	
Male/female	13/7
Risk factors for HCV:	
History of hospital admission	10
Blood transfusion	8
Operation	12
History of abnormal liver enzymes	7
Clinical	
Generalized weakness	10
Peripheral oedema	17
Hepatomegaly	4
Palpable purpura	7
Arthralgias	4
Arterial hypertension	5
Laboratory	
HCV-RNA in cryoprecipitates	15
Mixed cryoglobulinaemia	14
Rheumatoid factor	15
HCV-RNA	20
HCV-Ab	20
Histological	
Renal pathology	
MPGN	7
MN	2
Mesangioproliferative glomerulonephritis	1
Liver biopsy	
CAH	3
CPH	4
Skin biopsy	
Acral necrolytic erythema	2

MPGN, membranoproliferative glomerulonephritis; MN, membranous nephropathy; CAH, chronic active hepatitis; CPH, chronic persistent hepatitis.





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- **Anti-viral treatment protocol:**

Interferon-a2A was given subcutaneously in a dose of 3 MU three times weekly. The dose was adjusted according to patient tolerance. Patients were followed up weekly for 1 month and monthly thereafter for 12 months, Those with persistent HCV viraemia were given ribavirin in addition at a dose of 15 mgu kguday, with dose modification when indicated. Treatment was continued to the complete 12 months.

- **Renal response to anti-viral treatment :**

According to the renal response to anti-viral treatment, patients were divided into two groups: group I cases were

those who showed favourable response (stable or decreased serum creatinine and proteinuria), and group II cases were those who showed a deterioration in their serum creatinine and proteinuria. The two groups were compared to identify factors affecting the renal response to anti-viral treatment.

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Table 2. Biochemical characteristics (median and range) of the 20 HCV-infected patients before and after anti-viral therapy

	Before	After	*P*-value
Serum creatinine (mg/dl)	1.20 (1.01–1.67)	1.1 (0.81–2.25)	0.680
Proteinuria 24 h (g)	4 (3.04–4.77)	1.10 (0.86–2.25)	0.000
Haemoglobin (g/dl)	10.80 (10.17–12.51)	11.31 (10.30–12.16)	0.879
Serum albumin (g/dl)	2.5 (2.24–2.99)	3.55 (2.92–3.88)	0.012
ALT (IU/l)	33 (26.22–56.41)	25 (17.82–38.30)	0.153
AST (IU/l)	37 (31.99–52.01)	25 (24.05–41.83)	0.120
C3 (mg/dl)	89.5 (77.51–105.59)	111 (105.39–139.45)	0.005
C4 (mg/dl)	22	32	0.007
HCV viral titre (MEq/ml)	1.15 (1.02–8.13)	0.53 (0.42–4.17)	

Table 4. Adverse events of interferon and combined interferon–ribavirin therapy in patients with HCV-related glomerulopathy

Adverse events	Interferon therapy	Combined therapy
Temporary discontinuation of therapy	5	1
Dose reduction		
Due to anaemia	4	7
Due to other adverse events	–	–
Flu-like symptoms		
Headache	2	–
Fever	17	–
Gastrointestinal symptoms		
Anorexia	5	–
Vomiting	5	–
Nausea	5	–
Abdominal pain	1	–
Psychiatric symptoms		
Depression	1	1
Insomnia	1	1
Dermatological symptoms		
Alopecia	1	–

At 3 months after initiation of interferon treatment, only four of the 20 treated patients showed negative HCV-RNA-PCR. The 16 non-responders were given ribavirin. One of these showed response, while 15 showed persistent viraemia. Twelve months' antiviral treatment resulted in aviraemia in 25% of cases

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Table 3. Parameters at start of anti-viral treatment (median and confidence intervals) of patients with favourable renal response (group I) and those with unfavourable response (group II)

	Group I	Group II	*P*-value
Number	15	5	0.924
Age (years)	42 (36.81–48.76)	40 (24.71–57.29)	
Serum creatinine (mg/dl)	1.10 (0.89–1.43)	2.4 (1.30–3.10)	0.037
Proteinuria 24 h (g)	3.9 (2.7–4.9)	4 (1.90–5.4)	0.741
Serum albumin (g/dl)	2.8 (2.33–3.12)	2.00 (1.7–4.1)	0.395
HCV viral titre (MEq/ml)	1.15 (0.34–20.40)	4.93 (0.20–23.45)	0.750

Biochemical response to IFN therapy in such cases improved when combined with ribavirin . Further studies using higher doses or pegylated forms of IFN on HCV related MGN are urgently needed.

Antiviral Therapy for Hepatitis C Virus–Associated Mixed Cryoglobulinemia Vasculitis

A Long-Term Followup Study

David Saadoun,[1] Mathieu Resche-Rigon,[2] Vincent Thibault,[1] Jean-Charles Piette,[1] and Patrice Cacoub[1]

ARTHRITIS & RHEUMATISM
Vol. 54, No. 11, November 2006, pp 3696–3706

Table 2. Characteristics of all HCV-MC vasculitis patients and the 2 antiviral treatment groups at the end of therapy*

Parameter	All MC patients (n = 72)	Patients taking antiviral treatments: IFN alfa-2b plus ribavirin (n = 32)	PEG–IFN alfa-2b plus ribavirin (n = 40)	P
Age, years	59.86 ± 14.08	[illegible]	57.9 ± 12.41	0.13
Female, no. (%) of patients	37 (51.4)	16 (50)	21 (52.5)	1
HCV related				
Duration of HCV infection, years	27.34 ± 9.63	28.19 ± 11.2	26.73 ± 8.55	0.78
HCV genotype 1, no. (%)	44 (61.1)	16 (51.6)	28 (70)	0.14
HCV RNA, log copies/ml	5.87 ± 0.65	5.92 ± 0.57	5.83 ± 0.72	0.44
ALT, IU/liter	93.6 ± 54.4	83.2 ± 39.8	102 ± 63.0	0.38
Liver necroinflammation score (0–3 scale)†	1.3 ± 0.8	1.4 ± 0.9	1.3 ± 0.7	0.6
Liver fibrosis score (0–4 scale)†	1.9 ± 1.2	2.0 ± 1.1	1.8 ± 1.1	0.34
Cirrhosis, no. (%)	9 (12.5)	4 (13.3)	5 (12.5)	1
MC related				
Purpura, no. (%)	51 (73.9)	27 (87.1)	24 (63.2)	0.03
Peripheral neuropathy, no. (%)	[illegible]	[illegible]	27 (67.5)	0.23
Arthralgia, no. (%)	30 (41.7)	8 (25)	[illegible]	0.02
Renal involvement, no. (%)	22 (30.6)	12 (37.5)	10 (25)	0.23
Sicca syndrome, no. (%)	13 (18.1)	8 (25)	5 (13.2)	0.23
Myalgia, no. (%)	8 (11.1)	3 (9.4)	5 (12.5)	0.73
GI tract involvement, no. (%)	6 (8.3)	4 (12.5)	2 (5)	0.4
Raynaud's phenomenon, no. (%)	3 (4.2)	2 (6.2)	1 (2.5)	0.58
B cell lymphoma, no. (%)	9 (12.5)	4 (12.5)	5 (12.5)	1
Cryoglobulin level, gm/liter	1.15 ± 1.36	1.41 ± 1.49	0.93 ± 1.23	0.16
Type II cryoglobulins, no. (%)	51 (70.8)	26 (83.9)	25 (71.4)	0.26
Low C4 complement level, no. (%)	54 (75)	25 (78.1)	29 (72.5)	0.48
Treatment related				
Duration of anti-HCV therapy, months	16.63 ± 7.8	18.35 ± 10.0	13.25 ± 4.4	0.08
Ribavirin dosage, mg/day	915.9 ± 182.8	875.9 ± 195.7	[illegible] ± 169.3	0.5
Previous antiviral therapy, no. (%)	20 (27.6)	[illegible]	13 (32.5)	0.43
Corticosteroids, no. (%)	29 (40.3)	15 (46.9)	14 (35)	0.34
Plasmapheresis, no. (%)	9 (12.5)	[illegible]	[illegible]	0.01
Immunosuppressants, no. (%)	4 (5.6)	4 (12.5)	0 (0)	0.03
All adverse events, no. (%)	39 (54.2)	17 (53.1)	22 (55)	1
Outcome				
Deaths, no. (%)	8 (11.1)	[illegible]	[illegible]	0.98
Complete response, no. (%)‡				
Clinical	40 (55.5)	12 (37.5)	28 (70)	0.009
Virologic	49 (68.0)	19 (59.3)	30 (75)	0.20
Immunologic	33 (45.8)	9 (28.1)	24 (60)	0.009

* Except where indicated otherwise, values are the mean ± SD. HCV-MC = hepatitis C virus–associated mixed cryoglobulinemia; IFN = interferon; PEG = PEGylated; ALT = alanine aminotransferase; GI = gastrointestinal.
† Liver necroinflammation and fibrosis were graded according to the Metavir scoring system.
‡ Clinical, virologic, and immunologic responses were evaluated 12 months after the start of antiviral therapy.

EXTENDED REPORT

Peg-IFNα/ribavirin/protease inhibitor combination in hepatitis C virus associated mixed cryoglobulinemia vasculitis: results at week 24

David Saadoun,[1,2] M Resche Rigon,[3] V Thibault,[4] M Longuet,[1] S Pol,[5] F Blanc,[6] G Pialoux,[7] A Karras,[8] D Bazin-Karra,[9] C Cazorla,[10] D Vittecoq,[11] L Musset,[12] O Decaux,[13] J M Ziza,[14] O Lambotte,[15] Patrice Cacoub[1,2]

Table 1 Baseline characteristics of the 23 HCV-associated MC patients

Parameters	All n=23	Boceprevir n=8	Telaprevir n=15	p Value
Age	59 (52.5; 66)	59 (56.75; 68)	58 (51.5; 65.5)	0.33
Male gender (n,%)	12 (52.2)	4 (50)	8 (53.3)	1
HCV infection				
HCV genotype:				1
1b	13 (56.5)	5 (62.5)	8 (53.3)	
1a	9 (39.1)	3 (37.5)	6 (40)	
4	1 (4.3)	0	1 (6.7)	
Metavir liver fibrosis score:				0.51
Stage 1	2 (8.7)	0	2 (13.3)	
Stage 2	10 (43.5)	3 (37.5)	7 (46.7)	
Stage 3	4 (17.4)	1 (12.5)	3 (20)	
Stage 4	7 (30.4)	4 (50)	3 (20)	
Median baseline HCV RNA (log10 IU/ml)	6.2 (5.325; 6.53)	6.29 (5.292; 6.635)	6.07 (5.325; 6.485)	0.42
Median ALT level (IU/l)	52 (29; 70.5)	45 (28; 70.75)	53 (29.5; 68)	1
Haematologic variables				
Median haemoglobin count (g/dl)	13 (12.3; 14.65)	12.75 (12.6; 12.92)	13.6 (12.25; 14.75)	0.42
Median neutrophil count (/mm³)	3.03 (2.145; 4.18)	2.145 (1.775; 2.355)	3.74 (3.065; 4.68)	0.004
Median platelet count (/mm³)	159 (110; 197)	104.5 (91; 222.2)	159 (124.5; 191)	0.48
Previous response to antiviral therapy (PegIFNα/ribavirin)*				0.16
Naive	4 (17.4)	1 (12.5)	3 (20)	
No response	8 (34.8)	2 (25)	6 (40)	
Partial response	5 (21.7)	4 (50)	1 (6.7)	
Relapse	6 (26.1)	1 (12.5)	5 (33.3)	
MC related				
Type of cryoglobulinaemia:				0.53
Type II	20 (87)	8 (100)	13 (86.7)	
Type III	3 (13)	0	2 (13.3)	
Median serum cryoglobulin level (g/l)	0.443 (0.2; 0.845)	0.22 (0.1975; 0.719)	0.59 (0.305; 0.915)	0.32
Median serum C4 level (g/l)	0.09 (0.06; 0.13)	0.14 (0.1175; 0.24)	0.08 (0.06; 0.1)	0.013
Median serum rheumatoid factor levels (IU/ml)	60.5 (13; 145)	43 (13; 115)	61 (19; 165.5)	0.6
Vasculitis				
Purpura	16 (69.6)	6 (45)	10 (66.7)	1
Polyneuropathy	12 (52.2)	[illegible]	7 (46.7)	0.67
Arthralgia	9 (39.1)	1 (12.5)	8 (53.3)	0.09
Kidney involvement	6 (26.1)	1 (12.5)	5 (33.3)	0.37

Except where indicated otherwise values are median (IQR) and n (%).
*No response was defined as a reduction of less than 2log10 in HCV RNA; partial response was defined as a reduction of 2log10 or more in HCV RNA; relapse was defined as undetectable HCV RNA at the end of a previous course of therapy with HCV RNA positivity thereafter.
ALT, alanine aminotransferase; HCV, hepatitis C virus; MC, mixed cryoglobulinemia.

ACCESS

EXTENDED REPORT

Peg-IFNα/ribavirin/protease inhibitor combination in hepatitis C virus associated mixed cryoglobulinemia vasculitis: results at week 24

David Saadoun,[1,2] M Resche Rigon,[3] V Thibault,[4] M Longuet,[1] S Pol,[5] F Blanc,[6] G Pialoux,[7] A Karras,[8] D Bazin-Karra,[9] C Cazorla,[10] D Vittecoq,[11] L Musset,[12] O Decaux,[13] J M Ziza,[14] O Lambotte,[15] Patrice Cacoub[1,2]

Parameters	Baseline	Week 24	p Value
Clinical			
Purpura	16 (69.6)	1 (4.3)	0.003
Polyneuropathy	12 (52.2)	7 (30.4)	0.70
Arthralgia	9 (39.1)	1 (4.3)	0.045
Kidney involvement	6 (26.1)	1 (4.3)	0.11
Creatininemia (µmol/l)	112 (81–217)	83.5 (67–104)	0.12
Daily proteinuria (g)	0.55 (0.4–7.5)	0.2 (0–0.3)	0.005
Haematuria (n,%)	5 (21.7)	0	0.056
Median BVAS	9 (3–18)	0 (0–6)	p<0.0001
Virological			
Median HCV RNA (log10 IU/ml)	6.2 (5.32; 6.53)	1.1 (1.1; 1.1)	0.0006
HCV RNA detectable (n,%)	23 (100)	7 (30.4)	0.005
Median ALT level (IU/l)	52 (29; 70.5)	22.5 (20.25; 47)	0.09
Abnormal ALT level (n,%)	14 (60.9)	5 (31.2)	0.44
Immunological			
Median serum cryoglobulin level (g/l)	0.443 (0.2; 0.845)	0.06 (0; 0.2228)	0.0006
Cryoglobulin detectable (n,%)*	18 (100)	14 (77.8)	0.63
Median serum C4 complement level (g/l)	0.09 (0.06; 0.13)	0.15 (0.06; 0.1975)	0.045
Median serum rheumatoid factor (RF) levels (IU/ml)	60.5 (13; 145)	51.5 (17.5; 118.8)	0.43

Except where indicated otherwise values are median (IQR) and n (%).
*At inclusion, 18 out of 23 patients had detectable cryoglobulin.
ALT, alanine aminotransferase; BVAS, Birmingham Vasculitis Activity Score; HCV, hepatitis C virus; MC, mixed cryoglobulinemia.

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CASE REPORT

Long-term response to peginterferon in hepatitis C virus-associated nephrotic syndrome from focal segmental glomerulosclerosis

Hitesh H. Shah and Chinmay Patel

- The optimal therapy of HCV-associated FSGS is not currently known.
- A 47-year-old Hispanic male was referred by his primary care physician for evaluation of nephrotic range proteinuria.
- The rest of the examination was unremarkable.
- total protein was 4.3 g/dL, serum albumin was 1.9 g/dL,
- A24-h urine collection revealed 19.5 g of protein.
- HCV genotype testing showed genotype 1a.
- Patient was subsequently started on subcutaneous peginterferon alfa-2a 180 micrograms weekly for 12 months.
- At the completion of interferon treatment, spot urine total protein to creatinine ratio decreased to 1 and serum albumin returned to normal.
- His renal function continued to remain stable 5 years after completing interferon therapy with a serum creatinine of 2.1 mg/dL.
- His spot urine TP/CR ratio had further decreased to 0.2.
- His HCV RNA remained undetectable

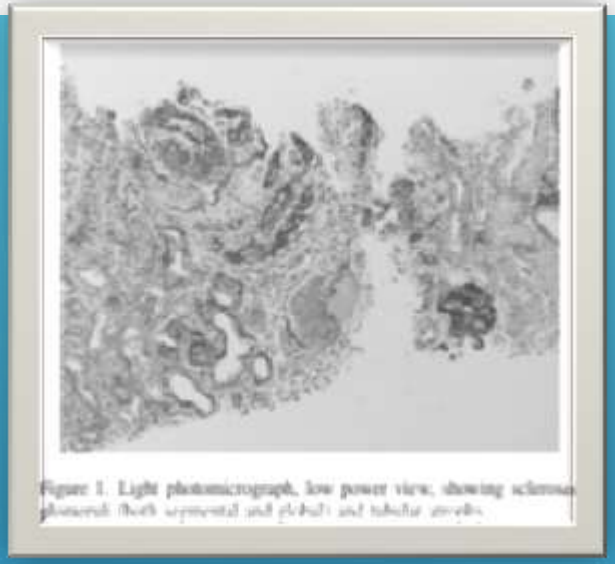


Figure 1. Light photomicrograph, low power view, showing sclerosis

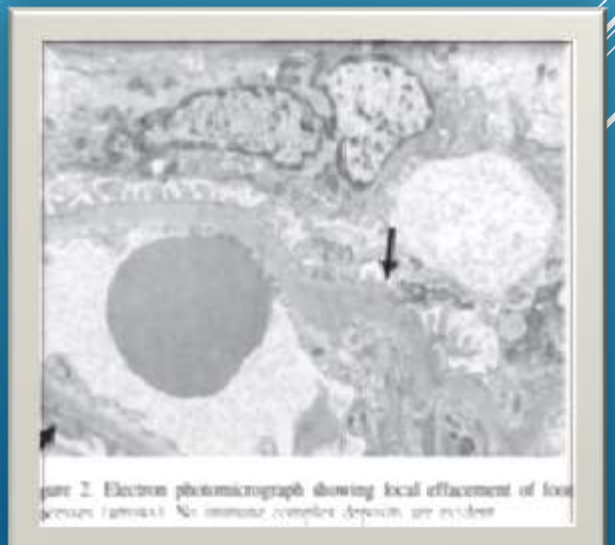
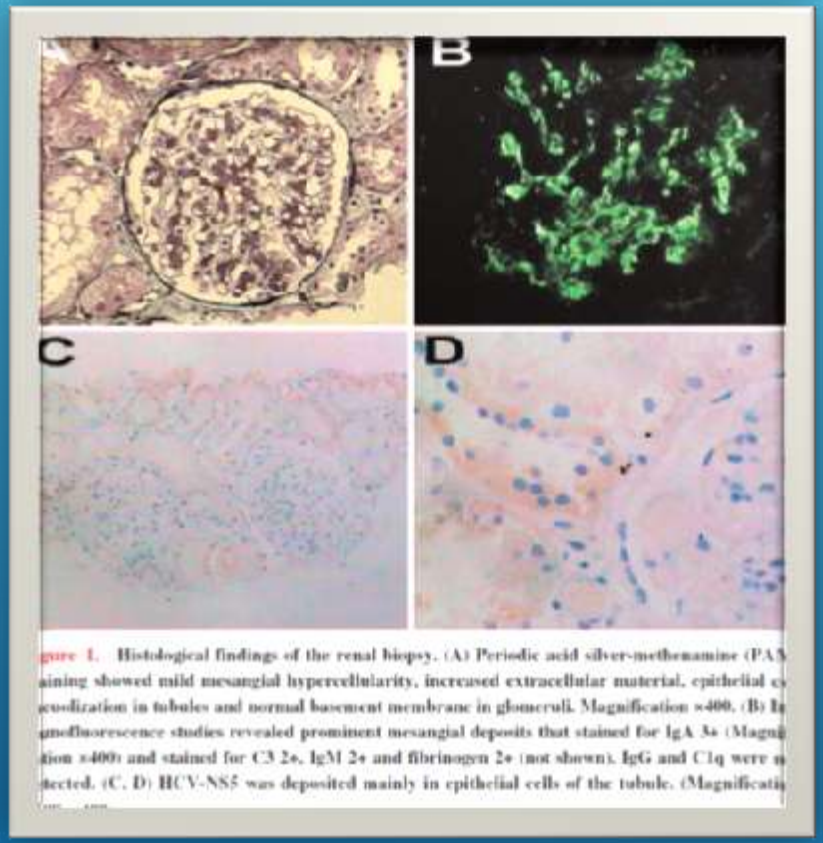


Figure 2. Electron photomicrograph showing focal effacement of foot

Successful Interferon-α Treatment in a Patient with IgA Nephropathy Associated with Hepatitis C Virus Infection

(Intern Med 49: 2531-2532, 2010)
(DOI: 10.2169/internalmedicine.49.4365)



gure 1. Histological findings of the renal biopsy. (A) Periodic acid silver-methenamine (PAS aining showed mild mesangial hypercellularity, increased extracellular material, epithelial c ecodization in tubules and normal basement membrane in glomeruli. Magnification ×400. (B) Ir unofluorescence studies revealed prominent mesangial deposits that stained for IgA 3+ (Magni ation ×400) and stained for C3 2+, IgM 2+ and fibrinogen 2+ (not shown). IgG and C1q were n tected. (C, D) HCV-NS5 was deposited mainly in epithelial cells of the tubule. (Magnificati

- A 35-year-old man
- Urinalysis showed proteinuria 2+ and hematuria 2+ and a 24-h urine collection demonstrated 1998 mg of protein.
- HCV antibody by ELISA and HCV RNA (genotype 2a) by PCR was detected in serum.
- Study of HCV-NS5 antigen showed granular deposition in epithelial cells of the tubules without deposition along glomerular capillary walls and/or mesangial region .
- A diagnosis of HCV-related IgA nephropathy was made.
- He was administered interferon-a (5 MU three times a week) and ribavirin (1,000 mg daily).
- His aminotransferase levels were normalized, and HCV RNA was undetectable at week 4.
- urinalysis showed proteinuria + - and blood negative and a 24-h urine protein was reduced to 162 mg.
- For 12 months of follow-up, he has remained free from systemic symptoms, with serum HCV RNA undetectable, and normal urinalysis and liver function

□ CASE REPORT □

Progressive Renal Failure and Blindness Due to Retinal Hemorrhage after Interferon Therapy for Hepatitis C Virus-associated Membranoproliferative Glomerulonephritis

Takayuki Suzuki, Katsuhiko Yonemura*, Takehiko Miyaji**, Hiroyuki Suzuki**, Reiko Takahira**, Yoshihide Fujigaki**, Taiki Fujimoto** and Akira Hishida**

Internal Medicine Vol. 40, No. 8 (August 2001)

Retinopathy consisting of retinal hemorrhage or cotton-wool spots are manifestation in more than 50% of treated patients .

(Kawano T, et al. AmJ Gastroenterol 1996)

These secondary disorders include:
1- Glomerulonephritis,
2-Acute interstitial nephritis
3- Retinopathy
4-Diabetes mellitus,
5- Interstitial pneumonitis
6-Thyroiditis,
7-Depression,
but these are usually reversible following discontinuation of IFN treatment .

(Okanoue T, J Hepatol 1996).

Mild and reversible retinopathy, manifesting as retinal hemorrhage or cotton-wool spots in more than 50% of patients receiving IFN (7), is usually noted within 8 weeks of the commencement of IFN treatment. Blindness, as observed in the present case, is rarely seen .

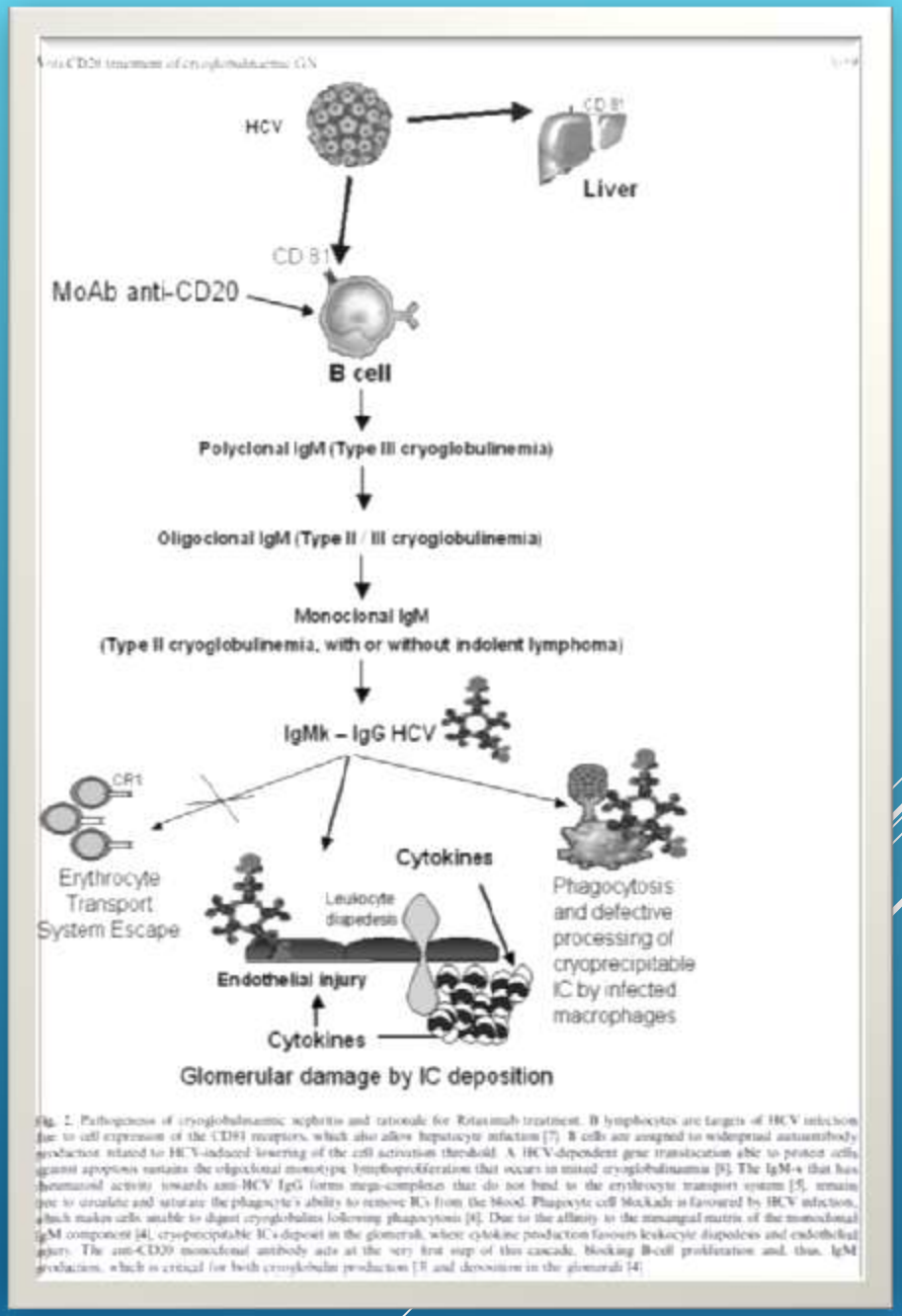
(Lohmann CP et al. Lancet 1999).

RITUXIMAB

- HCV eradication is obtained in no more than 50% of the patients , and the clinical benefit of antiviral treatment is often transient or restricted to patients with low-grade kidney involvement

- Rituximab is a chimeric monoclonal antibody directed against CD20, which results in rapid depletion of circulating and tissue B cells. Based on this mechanism of action, rituximab has the potential to deplete the expanded population of B cells that develop in HCV-associated vasculitis thereby reducing the production of pathogenic RF and formation of the cryoglobulin immune complex.

- CD20 is first expressed in the early pre–B cell stage, and it remains present until terminal differentiation into plasma cells.



Nephrol Dial Transplant (2004) 19: 3054–3061
doi:10.1093/ndt/gfh469
Advance Access publication 19 October 2004

Original Article

Nephrology Dialysis Transplantation

Long-term effects of anti-CD20 monoclonal antibody treatment of cryoglobulinaemic glomerulonephritis

Dario Roccatello[1–3], Simone Baldovino[1,3], Daniela Rossi[1,2], Morteza Mansouri[1,3], Carla Naretto[1,3], Mariella Gennaro[1,3], Roberto Cavallo[1], Mirella Alpa[1], Piera Costanzo[1], Osvaldo Giachino[1], Gianna Mazzucco[4] and Luigi Massimino Sena[1,3]

Table 1. Biochemical data of patients before Rituximab (at admission), 2, 6, 12 and 18 months after therapy

	SCr (mg/dl)	ESR	RF (IU/ml)	IgM (mg/dl)	C3 (mg/dl)	C4 (mg/dl)	Cryocrit (%)	Viral load (C × 10^6/dl)	ALT (IU/l)	Proteinuria (g/day)	TBP (g/dl)
Patient 1											
Admission	0.7	49	913	167	84	4	2	20	18	0.3	6.9
2 months	0.6	14	108	88	90	32	1	ND	14	0.1	7.0
18 months	0.7	16	72	101	88	17	1	9	20	0.1	7.1
Patient 2											
Admission	1.2	78	178	528	80	4	3	1.8	26	4.5	6.3
2 months	1.1	58	83	451	112	6	1	0.4	22	0.6	6.5
6 months	1.2	51	97	445	105	5	2	1	18	0.1	6.7
12 months	1.7	88	87	431	111	3	1	ND	23	0.1	6.8
18 months	1.7	88	127	429	107	6	0	ND	15	0.1	7.1
Patient 3											
Admission	1.0	103	2244	1909	39	0	5	9.6	21	2.1	5.6
2 months	0.8	80	720	607	56	11	3	2.2	16	1.2	5.8
6 months	0.7	37	135	237	55	10	1	2.5	28	0.3	6.2
12 months	0.8	12	415	202	66	2	0	1.5	34	0.1	6.0
Patient 4											
Admission	0.8	72	165	1175	99	3	6	3	18	1	6.7
2 months	1	53	112	727	10	4	2	2.3	23	0.8	7.0
6 months	0.7	27	40	753	85	11	2	ND	24	0.4	7.0
12 months	0.8	46	39	794	93	13	2	2.1	19	0.3	6.8
18 months	0.8	37	131	751	92	12	0	ND	26	0.3	7.1
Patient 5											
Admission	6.8	54	298	397	65	4	4	1.3	15	3.5	6.5
2 months	4.6	30	24	80	80	11	2	0.8	17	0.9	6.5
6 months	4.9	19	30	60	78	28	0.5	1.0	16	0.6	6.5
12 months	5.0	19	249	142	79	16	0	0.7	44	0.6	7.5
Patient 6											
Admission	1.4	40	90	331	83	3	0.5	1.8	66	1.7	6.4
2 months	1.0	10	59	230	71	12	0.5	ND	58	0.2	6.9
6 months	0.5	6	58	195	69	21	0	1.7	43	0.1	7.1
12 months	0.6	4	135	299	75	2	0	0.9	213	0	7.5

SCr, serum creatinine; ESR, erythrocyte sedimentation rate; RF, rheumatoid factor; ALT, alanine aminotransferase; TBP, total blood proteins; ND, not determined.
Viral load was measured by branched DNA and expressed as viral copies/ml.

Rheumatology 2006;45:842–846
Advance Access publication 17 January 2006

doi:10.1093/rheumatology/kel004

Rituximab treatment for glomerulonephritis in HCV-associated mixed cryoglobulinaemia: efficacy and safety in the absence of steroids

L. Quartuccio, G. Soardo[1], G. Romano, F. Zaja[2], C. A. Scott[3], G. De Marchi, M. Fabris, G. Ferraccioli[4] and S. De Vita

TABLE 1. Characteristics of the patients at baseline

	Patient 1	2	3	4	5	Mean ± S.D.
Gender	F	F	F	M	F	–
Age (yr)	58	45	62	56	65	57 ± 7.7
HCV genotype	1b	1b	1b	2a/2c	2a/2c	–
Hepatitis diagnosis (year)	1992	1993	1990	1994	1993	–
Liver biopsy	Chronic hepatitis	Cirrhosis	Cirrhosis	Chronic hepatitis	Chronic hepatitis	–
Bone marrow biopsy	LPD	LPD	Not involved	Not involved	Not involved	–
Serum cryoglobulins (mg/dl)	3550	2434	2993	3283	45	2532 ± 1472
RF (IU/ml)	418	3910	3710	731	146	1888.8 ± 1802.6
IgM (mg/dl)	433	400	437	194	472	387.2 ± 111.0
C4 (mg/dl)	2	4	12	10	3	5.4 ± 4.4
FcγRIIIa genotype	VV	VF	VF	VF	VF	–
Previous therapy for nephritis	PEG-interferon, PE, CYC	Interferon, PEG-interferon	None	None	None	–
Other clinical features	Neuropathy, purpura, fever	Purpura, arthralgias	Neuropathy	Purpura	Purpura	–
ALT (IU/l)	76	14	33	146	48	–
Nephritis duration (months)	18	65	19	8	48	31.6 ± 23.9
Renal biopsy	not done	GN MBP	GN MBP	GN MGP	GN MBP	–
GFR (ml/min)	22.7	23.8	57.0	66.7	50.0	48.2 ± 26.6
Creatinine (mg/dl)	2.3	1.8	0.9	1.4	1.0	1.5 ± 0.6
Proteinuria (mg/24 h)	2204	651	1500	680	3700	1747.0 ± 1267.3
Urinary sediment	Active	Active	Active	Active	Active	–

TABLE 2. Laboratory features of the patients during the follow-up

	Creatinine (mg/dl)	GFR (ml/min)	Proteinuria (mg/24 h)/ urinary sediment[b]	RF (IU/ml)	IgM (mg/dl)	Cryos (mg/dl)	C4 (mg/dl)	CD19 % BM	CD19 % PB	ALT (IU/l)
Patient 1										
0	2.3	22.7	2204/active	418	433	3550	2	3.5%	3%	76
+2	1.64	31.8	126/inactive	–	222	1803	2	–	–	33
+6	1	52.2	72/inactive	58	27	177	4	0%	0%	26
+9	0.9	58.0	39/inactive	49	56	150	5	–	–	16
+12	0.98	53.7	60/inactive	128	65	0	6	–	–	5
+15	0.86	60.1	51/inactive	52	83	0	2	–	14%	9
last follow-up (+18)	0.97	53.7	90/inactive	70	107	0	9	–	18.6%	1
Patient 2[a]										
0	1.85	23.8	651/active	3910	400	2434	8	10%	6%	14
+2	1.18	37.0	279/microhaem.	96	–	–	1	–	–	2
+6	1.7	25.9	105/microhaem.	345	159	3150	1	2%	2%	2
+9	1.9	22.2	457/microhaem.	–	376	4846	5	–	–	4
last follow-up	1.4	34.4	9/microhaem.	288	149	1261	5	–	0%	27
Patient 3[a]										
0	0.88	48.8	1500/active	3710	437	2993	12	7%	4%	33
+2	1.3	28.8	182/inactive	5200	326	2780	9	–	–	29
+6	0.63	66.5	54/inactive	2430	383	1842	5	7%	0%	31
+9	0.8	48.6	186/inactive	2990	415	2965	5	–	0%	26
+12	0.66	59.8	50/inactive	2420	301	4047	6	–	0%	24
+15	0.87	48.8	43/inactive	1190	290	4638	4	–	–	30
+21	1	38.1	173/inactive	8370	379	–	4	–	–	41
last follow-up	0.89	42.9	64/inactive	2300	279	3954	4	–	6%	18
Patient 4										
0	1.38	86.0	680/active	1260	194	3638	2	27%	20%	146
+2	1	119.1	114/inactive	322	170	1961	3	–	–	39
+6	1	120.1	225/microhaem.	515	110	1354	4	–	1%	109
+9	0.9	130.1	375/microhaem.	257	106	1954	5	–	6%	109
last follow-up	1.26	95.2	557/active	117	139	3316	2	–	7%	27
Patient 5										
0	1	50.0	3700/active	146	472	45	3	13%	10%	48
+2	0.9	55.5	1800/active	39	233	248	4	–	–	44
+6	1	50.0	900/microhaem.	46	201	41	9	3%	1%	33
+9	0.8	62.5	570/inactive	20	115	99	8	–	0%	26
+12	0.85	59.0	324/inactive	20	99	181	13	–	–	22
Last follow-up (+15)	0.9	61.0	300/inactive	22	89	171	16	–	0%	26

Normal values/ranges: RF, <15 IU/ml; creatinine, <1.3 mg/dl; C4, 10–40 mg/dl; IgM, 40–230 mg/dl.

[a]These patients suffered from decompensated liver cirrhosis. A transient increase in creatinine level was documented at months +6 and +9 in patient 2 and at month +2 in patient 3 due to hypovolaemic state; renal function rapidly improved in both patients after rehydration, with creatinine values of 1.3–1.4 mg/dl in patient 2 and 0.7–0.9 mg/dl in patient 3.

[b]Urinary sediment: active = microhaematuria (>10 red blood cells per high-power field) and casts; microhaem. = microhaematuria without casts; inactive = neither microhaematuria nor casts. GFR, glomerular filtration rate; cryos, serum cryoglobulins concentration; BM, bone marrow; PB, peripheral blood; ALT, alanine aminotransferase (normal range 10–45 IU/l).

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Review

Treatment with rituximab in patients with mixed cryoglobulinemia syndrome: Results of multicenter cohort study and review of the literature

C. Ferri [a,*], P. Cacoub [b], C. Mazzaro [c], D. Roccatello [d], P. Scaini [e], M. Sebastiani [a], A. Tavoni [f], A.L. Zignego [g], S. De Vita [h]

Table 1
Demographic and clinico-serogical features of 87 MC patients treated with rituximab.

Patients no	87	
M/F	19/68	
Mean age (years ± SD)	62.3 ± 11.4	
Disease duration (years ± SD)	9 ± 6.2	
HCV-associated MC	80	92%
Essential MC	5	6%
MC overlapping with CTD*	2	2%
Cryoglobulin characterization		
Type II	73	84%
Type III	14	16%
Cryocrit (range^)	<0.5 - 26%	
Low C4°	63	72%
Clinical manifestations		
Chronic hepatitis	52	60%
Purpura	51	59%
Renal inv. (MPGN)	38	44%
Peripheral neuropathy	69	79%
Vasculitic skin ulcers	24	28%
B-cell NHL	6	7%
Abdominal vasculitis	1	1%
Main indication to rituximab		
MPGN	26	30%
Skin vasculitis	22	25%
Severe purpura	8	9%
Non-healing ulcers	14	16%
Peripheral neuropathy)	20	23%
B-cell NHL	6	7%
Abdominal vasculitis	1	1%
Multiple symptoms	12	14%

MPGN: membranoproliferative glomerulonephritis.
* CTD: connective tissue diseases.
^ Trace amount of cryoglobulins: cryocrit < 0.5%.
° Undetectable or under lower limit of normal range.

Table 2
Effects of rituximab treatment in 87 patients with active MCs.

		After 6-month from Rituximab cycle		
	Pts no.	CR	PR	NR
Purpura	51	38 (74%)	4 (8%)	9 (18%)
Vasculitic skin ulcers	24	14 (58%)	7 (29%)	3 (12%)
Peripheral neuropathy	69	30 (44%)	18 (26%)	20 (29%)
MPGN	38	19 (50%)	17 (45%)	2 (5%)
NHL-B	6	3 (50%)	2 (33%)	1 (17%)
Abdominal vasculitis	1	1 (100%)	0	0
Cryocrit	87	26 (30%)	17 (19%)	44 (51%)
Low C4	63°	18 (29%)	13 (21%)	32 (50%)

*Adverse events**	
Total	18 (21%)
Infusion-related reactions	4 (5%)°
Infections	4 (5%)**
Mild adverse events	8 (9%)^^
Worsening of MC syndrome	2 (2%)°°
Drop out due to adverse events	4 (5%)§

CR: complete response; PR: partial response; NR: non-responders.
NHL-B: Non-Hodgkin's B-cell lymphoma.
^ Undetectable or under lower limit of normal range.
* Severe adverse events 3 pts: serum sickness-like reaction, infectious pneumonia, gangrene.
° Infusion-related reactions: hypotension (2), urticaria (1), serum sickness-like reaction (1).
** Infections: urinary tract infection (2), infectious pneumonia (1), gangrene (1).
°° Worsening of severe skin vasculitis (1 pt) or peripheral neuropathy (1 pt).
^^ Mild manifestations: neutropenia (2), hypogammaglobulinemia (5), hypertransaminasemia(1).
§ Drop out: worsening of vasculitis (1), serum sickness-like reaction (1), severe infections (2).

Review

Anti-CD20 monoclonal antibody (rituximab) treatment for cryoglobulinemic vasculitis: where do we stand?

P Cacoub, A Delluc, D Saadoun, D A Landau, D

Ann Rheum Dis 2008;**67**:283–287. doi:10.1136/ard.2006.065565

Table 1 Main baseline characteristics of patients with cryoglobulinemia vasculitis who received anti-CD20 antibody (rituximab) treatment

	No. of patients with available data	No. of positive patients	Positive patients (%)
Age (years), mean (range),	57	–	[illegible]
Sex (f)%	57	45	79
Vasculitis :			
Duration (months), mean (range)	57	–	60.1 (6–240)
Skin involvement	57	48	84.2
Arthralgia	57	35	61.4
Neuropathy	57	31	[illegible]
Glomerulonephritis	57	18	31.6
Immunology:			
Cryoglobulin positive	57	57	100
Type I		2	3.5
Type II		41	71.9
Type III		10	17.6
Type unknown		4	7.0
Rheumatoid factor positive	57	30	52.6
C4 serum level (mg/dl), mean	57	–	7.1
HCV status	57		
HCV RNA negative or unknown		14	24.6
HCV RNA positive		43	75.4
Genotype 1–4		24	55.8
Genotype 2–3		18	41.9
Genotype not available		1	2.3
Viral load >2 million IU/mL	8	6	75.0
ALT (IU/L), mean	31	–	54.3
Previous treatment			
HCV infection	37		
Interferon α		27	72.8
Pegylated interferon α plus ribavirin		4	14.8
None		12	32.4
Vasculitis treatment:			
Corticosteroids	36*	31	86.1
Immunosupressive drug	56	18	32.1
Plasma exchange	56	12	21.4

Table 2 Main course of cryoglobulinemia vasculitis features after anti-CD20 antibody (rituximab) infusion

	No. of patients positive at baseline	No. of patients with available data at follow up	Patients with available data at follow up (%)
Vasculitis:			
Skin involvement	48	40	
CR	–	27	67.5
PR	–	5	12.5
NR	–	8	20.0
Arthralgia	35	34	
CR	–	18	52.9
PR	–	9	26.5
NR	–	7	20.6
Neuropathy	31	29	
CR	–	9	31.0
PR	–	18	62.1
NR	–	2	6.9
Glomerulonephritis	18	18	
CR	–	12	66.6
PR	–	3	16.7
NR	–	3	16.7
Cryoglobulin	57	22*	
CR	–	16	72.7
PR	–	2	9.1
NR	–	4	18.2
Follow up after rituximab therapy:			
Duration (months), mean (range)	57	56	9.7 (0.3–24)
Relapses	–	14 out of 36	39

*The serum cryoglobulin status at the end of follow-up was available in 22 patients.
CR, complete response; NR, non-response; PR, partial response.

Review

Anti-CD20 monoclonal antibody (rituximab) treatment for cryoglobulinemic vasculitis: where do we stand?

P Cacoub, A Delluc, D Saadoun, D A Landau, D Sene

- A relatively small number of side effects

1- Bradycardia

2-Hypotension

3- Infection (in three renal transplant patients)

4-Mild alanine aminotransferase (ALT) elevation

5-Retinalarterial thrombosis

6- Panniculitis of elbows and knees

7-Serum sickness

8- Two deaths were reported; one occurred 12 months after rituximab infusion in an HCV-infected patient with renal insufficiency, and the second occurred 2 months after rituximab infusion in an HCV-negative renal transplant patient due to Cryptococcus neoformans.

RITUXIMAB WITH OR WITHOUT PEGYLATED INTERFERON ALFA-2B PLUS RIBAVIRIN

ARTHRITIS & RHEUMATISM
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Efficacy and Tolerability of Rituximab With or Without PEGylated Interferon Alfa-2b Plus Ribavirin in Severe Hepatitis C Virus–Related Vasculitis

A Long-Term Followup Study of Thirty-Two Patients

Benjamin Terrier,[1] David Saadoun,[1] Damien Sène,[2] Jérémie Sellam,[3] Laurent Pérard,[4] Brigitte Coppéré,[4] Alexandre Karras,[5] François Blanc,[6] Matthias Buchler,[7] Emmanuelle Plaisier,[8] Pascale Ghillani,[2] Michelle Rosenzwajg,[9] and Patrice Cacoub[1]

Table 1. Baseline characteristics of the patients with chronic active HCV-related vasculitis, according to treatment*

Characteristic	All patients (n = 32)	Rituximab with PEG–IFN alfa-2b plus ribavirin (n = 20)	Rituximab only (n = 12)
No. of men/no. of women	14/18	6/14	8/4
Age, mean ± SD years	59 ± 12	61 ± 11	57 ± 13
HCV related			
Genotype 1	16 (52)	12 (63)	4 (34)
Genotype 2	7 (23)	4 (21)	3 (25)
Genotype 3	5 (16)	2 (11)	3 (25)
Genotype 4	1 (3)	0 (0)	1 (8)
Genotype 5	2 (6)	1 (5)	1 (8)
Genotype not available	1	1	0
HCV RNA, mean ± SD log copies/IU	5.9 ± 0.6	5.8 ± 0.5	6.1 ± 0.8
Vasculitis duration, mean ± SD months	31 ± 42	28 ± 46	36 ± 35
METAVIR score, mean ± SD			
Activity score	1.4 ± 0.9	1.4 ± 1.0	1.4 ± 0.5
Fibrosis score	2.2 ± 1.4	2.3 ± 1.4	2.0 ± 1.4
MC related			
Cryoglobulin positivity	29 (91)	18 (90)	11 (92)
Cryoglobulin level, mean ± SD gm/liter	1.03 ± 0.78	1.25 ± 0.78†	0.66 ± 0.63
Type II cryoglobulins	28 (97)	18 (100)	10 (91)
Monoclonal kappa	27 (96)	18 (100)	9 (90)
Monoclonal lambda	1 (4)	0 (0)	1 (10)
Type III cryoglobulins	1 (3)	0 (0)	1 (9)
C4, mean ± SD gm/liter	0.08 ± 0.09	0.08 ± 0.10	0.09 ± 0.09
RF positivity	28/31 (90)	17/19 (89)	11/12 (92)
RF, mean ± SD IU/liter	236 ± 387	182 ± 224	329 ± 573
IgM, mean ± SD gm/liter	2.5 ± 3.2	2.0 ± 1.1	3.1 ± 4.4
Vasculitis-related organ involvement			
Purpura	22 (69)	14 (70)	8 (67)
Peripheral nervous system	22 (69)	16 (80)	6 (50)
Arthralgia	17 (53)	11 (55)	6 (50)
Kidney	14 (44)	10 (50)	4 (33)
Myalgia	6 (19)	3 (15)	3 (25)
Gastrointestinal tract	3 (9)	3 (15)	0 (0)
Heart	3 (9)	2 (10)	1 (8)
Central nervous system	2 (6)	2 (10)	0 (0)
B cell non-Hodgkin's lymphoma	8 (25)	4 (20)	4 (33)
Treatment			
Rituximab with PEG-IFN alfa-2b plus ribavirin	20 (63)	20	0
Antiviral-naive patients	9	9	–
Antiviral-resistant or antiviral-relapser patients	11	11	–
Rituximab only	12 (37)	–	12

* Except where indicated otherwise, values are the number (%) of patients. HCV = hepatitis C virus; PEG–IFN alfa-2b = PEGylated interferon alfa-2b; MC = mixed cryoglobulinemia; RF = rheumatoid factor.
† $P = 0.04$ versus rituximab only.

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Benjamin Terrier,[1] David Saadoun,[1] Damien Sène,[2] Jérémie Sellam,[3] Laurent Pérard,[4] Brigitte Coppéré,[4] Alexandre Karras,[5] François Blanc,[6] Matthias Buchler,[7] Emmanuelle Plaisier,[8] Pascale Ghillani,[2] Michelle Rosenzwajg,[9] and Patrice Cacoub[1]

Table 2. Clinical, immunologic, and virologic efficacy of therapy*

	Rituximab with PEG–IFN alfa-2b plus ribavirin (n = 20)	Rituximab only (n = 12)
Clinical response		
Complete	16/20 (80)	7/12 (58)
Partial	3/20 (15)	1/12 (9)
Nonresponder	1/20 (5)	4/12 (33)
Relapse	3/20 (15)	4/12 (33)
Immunologic response		
Complete	12/18 (67)	5/11 (46)
Partial	6/18 (33)	4/11 (36)
Nonresponder	0/18 (0)	2/11 (18)
Relapse	5/18 (28)	6/12 (50)
Virologic response		
Sustained	11/20 (55)	0/12 (0)
Nonresponder	9/20 (45)	12/12 (100)

* Values are the number (%) of patients. None of the differences were significant. PEG–IFN alfa-2b = PEGylated interferon alfa-2b.

Efficacy of treatment.

Clinical improvement was observed after a mean SD period of 6.8 4.7 months for patients treated with rituximab and PEG–

IFN alfa-2b plus ribavirin and 3.5 1.3 months for those treated with rituximab alone;

Immunologic response in these patients was observed after a mean SD period of 7.0 3.3 months and 5.0 2.1 months, respectively.

No difference was observed regarding the clinical, immunologic, and virologic efficacy of rituximab and PEG–IFN alfa-2b plus ribavirin between antiviral-naive pa-tients and antiviral-resistant or antiviral-relapser

patients, except for a trend toward more frequent complete immunologic responses in antiviral-resistant or antiviral-relapser patients (complete response in 90% and partial response in 10%) than in antiviral-naive

patients (complete response in 38% and partial response

in 62%; *P* 0.07).

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Efficacy and Tolerability of Rituximab With or Without PEGylated Interferon Alfa-2b Plus Ribavirin in Severe Hepatitis C Virus–Related Vasculitis

A Long-Term Followup Study of Thirty-Two Patients

Benjamin Terrier,[1] David Saadoun,[1] Damien Sène,[2] Jérémie Sellam,[3] Laurent Pérard,[4] Brigitte Coppéré,[4] Alexandre Karras,[5] François Blanc,[6] Matthias Buchler,[7] Emmanuelle Plaisier,[8] Pascale Ghillani,[2] Michelle Rosenzwajg,[9] and Patrice Cacoub[1]

7 patients experienced a clinical relapse (22%),

11 patients experienced a immunological relapse .

rituximab and PEG–IFN alfa-2b plus ribavirin	rituximab	rituximab and PEG–IFN alfa-2b plus ribavirin	rituximab
3 (15%)	4 (33%) (*P* 0.34)	5 patients treated	6 patients treated

All clinical relapses were associated with an immunologic relapse.
All clinical and immunologic relapsers (n 11) were HCV RNA positive
Six patients were re-treated with rituximab. Among these 6 patients, 5 had an immunologic and clinical relapse, and 1 had only an immunologic relapse.

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B cell depletion and B cell recovery were correlated with the clinical and immunologic responses.

B cell depletion was associated with a clinical response in 92% of patients and with an immunologic response in 96% of patients, while the absence of B cell depletion was associated with the absence of clinical and immunologic responses.

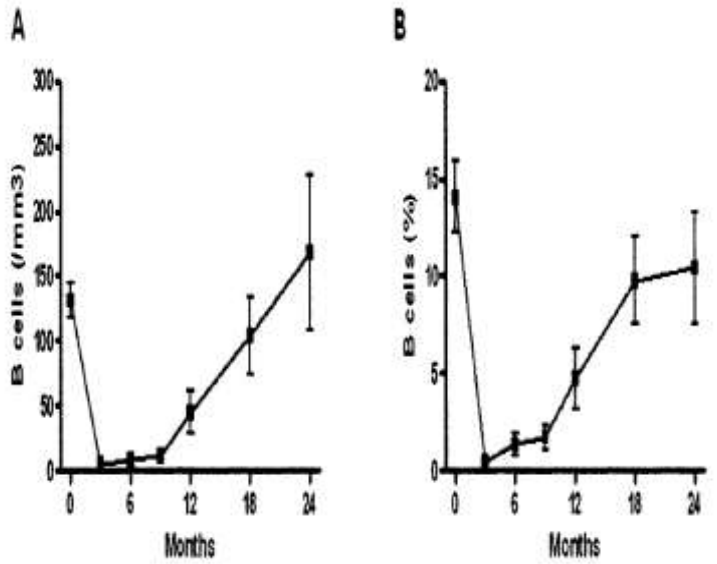

Figure 1. Dynamics of CD19+ B cell depletion and recovery during and after treatment with rituximab in patients with hepatitis C virus–related vasculitis. Values are the mean ± SD absolute number of CD19+ cells per mm^3 (A) and the mean ± SD percentage of CD19+ cells among total lymphocytes (B).

The NEW ENGLAND JOURNAL of MEDICINE

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ORIGINAL ARTICLE

Regulatory T-Cell Responses to Low-Dose Interleukin-2 in HCV-Induced Vasculitis

David Saadoun, M.D., Ph.D., Michelle Rosenzwajg, M.D., Ph.D., Florence Joly, Ph.D., Adrien Six, Ph.D., Fabrice Carrat, M.D., Ph.D., Vincent Thibault, Pharm.D., Damien Sene, M.D., Ph.D., Patrice Cacoub, M.D., and David Klatzmann, M.D., Ph.D.

- Patients with HCV-cryovas have been shown to have a reversible quantitative defect of the CD4+CD25++FoxP3+ regulatory T cells (Tregs) .

  Saadoun D et al. Blood 2008.

- Interleukin 2 (IL-2), a cytokine that promotes Treg survival and function, could be beneficial for patients who are resistant to HCV therapy.

  Saadoun D N Engl J Med 2011

- Ten patients with HCV-cryovas that was refractory to conventional antiviral and/or rituximab therapy received one IL-2 course of 1.5 million IU/day for 5 days, followed by three 5-day courses of 3 million IU/day at weeks 3, 6 and 9.

Characteristic or Outcome	Patient 10
Age at diagnosis (yr)	43
Sex	Female
Symptoms	
At baseline	Arthralgia, purpura, neuropathy, kidney involvement, fatigue
After administration of interleukin-2	Neuropathy
Previous therapy	Peginterferon alfa, ribavirin/rituximab
Serum cryoglobulin (g/liter)	
At baseline	0.40
After administration of interleukin-2	0.61
C4 complement (mg/liter)	
At baseline	0.043
After administration of interleukin-2	0.034
HCV genotype	1
HCV viral load (log copies/ml)	
At baseline	3.45
After administration of interleukin-2	3.61
Treatment side effects*	
Course 1	—
Course 2	Flulike syndrome, local reaction
Course 3	—
Course 4	—

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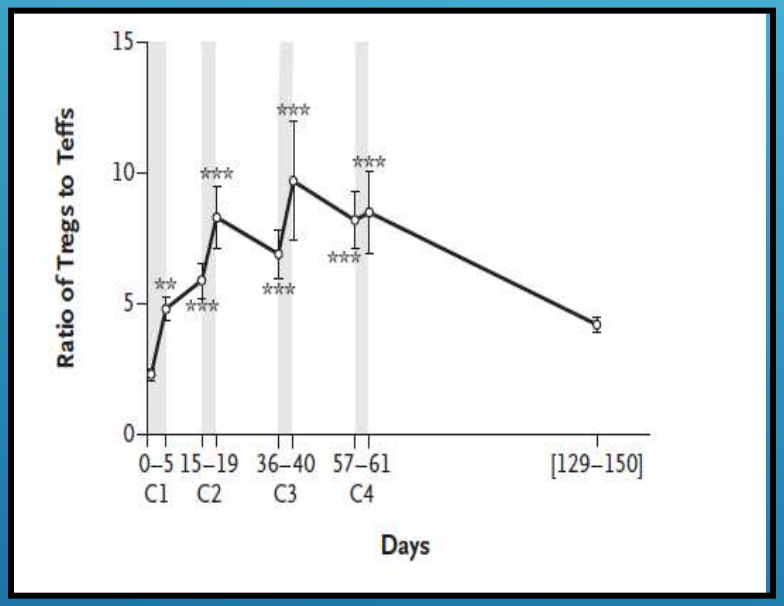

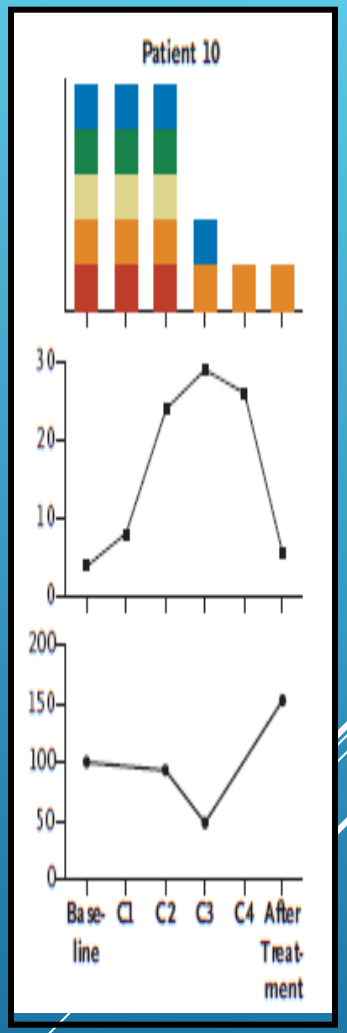

ARD Online First, published on August 6, 2013 as 10.1136/annrheumdis-2013-203883

Hepatitis C virus-induced vasculitis: therapeutic options

Patrice Cacoub,[1,2,3,4] Benjamin Terrier,[5] David Saadoun[1,2,3,4]

Therapeutic Strategies in HCV-related Cryoglobulinemic Vasculitis

Mild to Moderate disease	Severe disease	Life threatening
(Purpura, arthralgia, polyneuropathy)	(Progressive renal disease, mononeuritis multiplex, skin ulcer)	(Rapidly progressive nephritis, CNS, digestive and/or pulmonary involvement)
Peg IFN-α + Ribavirin	Rituximab Peg IFN-α + Ribavirin	Steroids, plasma exchange, cyclophosphamide and/or rituximab. Peg IFN-α + Ribavirin (differed)

9.2: Hepatitis C virus (HCV) infection–related GN

(Please also refer to the published KDIGO Clinical Practice Guidelines for the Prevention, Diagnosis, Evaluation, and Treatment of Hepatitis C in Chronic Kidney Disease.)

9.2.1: For HCV-infected patients with CKD Stages 1 or 2 and GN, we suggest combined antiviral treatment using pegylated interferon and ribavirin as in the general population. (*2C*) [based on KDIGO HCV Recommendation 2.2.1]

9.2.1.1: Titrate ribavirin dose according to patient tolerance and level of renal function. (*Not Graded*)

9.2.2: For HCV-infected patients with CKD Stages 3, 4, or 5 and GN not yet on dialysis, we suggest monotherapy with pegylated interferon, with doses adjusted to the level of kidney function. (*2D*) [based on KDIGO HCV Recommendation 2.2.2]

9.2.3: For patients with HCV and mixed cryoglobulinemia (IgG/IgM) with nephrotic proteinuria or evidence of progressive kidney disease or an acute flare of cryoglobulinemia, we suggest either plasmapheresis, rituximab, or cyclophosphamide, in conjunction with i.v. methylprednisolone, and concomitant antiviral therapy. (*2D*)

CONCLUSION

- The interplay between HCV and the kidney is complex.
- In MPGN type I and cryoglobulinemic glomerulonephritis, there is considerable circumstantial evidence for an etiologic link between the viral infection and the renal injury.
- For many of the others, it could be argued that the reported cases represent chance associations of relatively common maladies rather than examples of causal linkage.
- we recommend that all HCV-infected patients with evidence of renal dysfunction receive a careful and thorough clinical evaluation, including renal biopsy where clinically feasible.

CONCLUSION

- The cornerstone of HCV therapy has been and continues to be interferon-a, which has the potential to exacerbate autoimmune disease states .

- Advances using a triple combination with pegylated interferon-a (Peg-IFN-a), ribavirin and a protease inhibitor in patients infected by the genotype 1 virus have shown promising results.

- In more severe cases, combination therapy with rituximab and optimal HCV treatment appears logical, as it may target both mixed cryoglobulin (MC) producing B cells and the viral trigger.

THANK YOU